MEMORIAL HOSPITAL NUMBER

DELAWARE STATE MEDICAL JOURNAL

Official Organ of the Medical Society of Delaware
INCORPORATED 1789

VOLUME 25
NUMBER 10

OCTOBER, 1953

Per Year, $4.00
Per Copy $ .50

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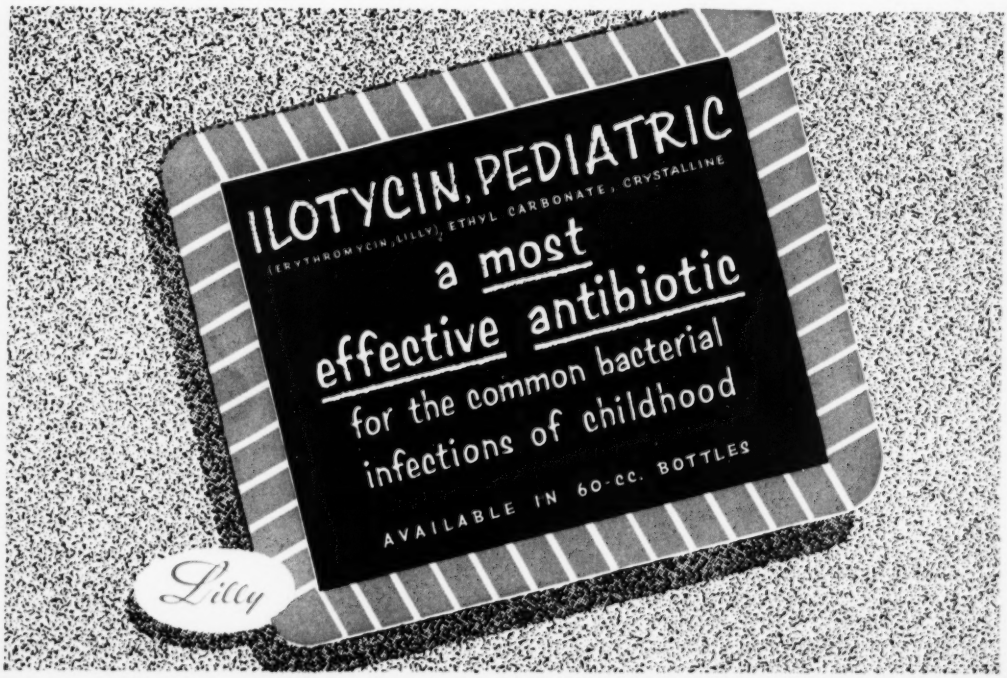
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Entered as second-class matter June 28, 1929, at the Post Office at Wilmington, Delaware, under the Act of March 3, 1879. Editorial Office, 822 North American Building, Wilmington 7, Delaware. Business Office, Farnhurst, Delaware. Issued monthly. Copyright, 1953, by the Medical Society of Delaware.



The Journal of the American Chemical S

VOL. 50 FEBRUARY, 1928

A QUARTER OF A

[Contribution from the Research Laboratories of Parke, Davis and Co.]

THE ACTIVE PRINCIPLES OF THE POSTERIOR LOBE OF THE PITUITARY GLAND.[1] I. THE DEMONSTRATION OF THE PRESENCE OF TWO ACTIVE PRINCIPLES. II. THE SEPARATION OF THE TWO PRINCIPLES AND THEIR CONCENTRATION IN THE FORM OF POTENT SOLID PREPARATIONS

By Oliver Kamm, T. B. Aldrich, J. W. Grote, L. W. Rowe and E. P. Bugbee

Received December 31, 1927 Published February 4, 1928

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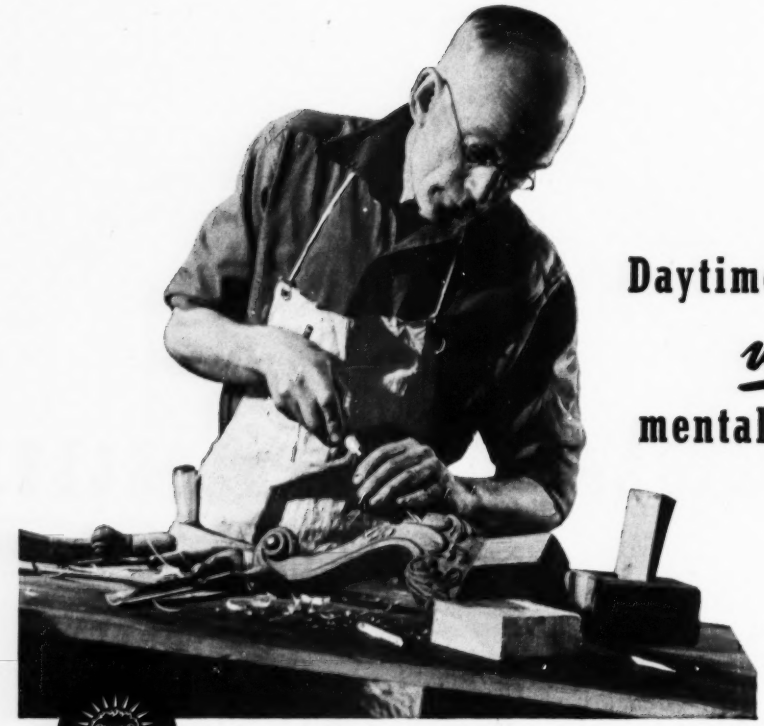
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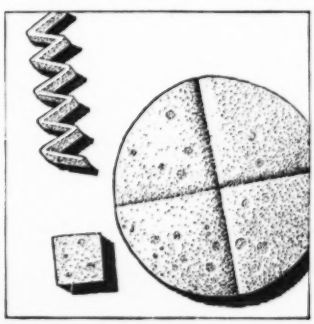
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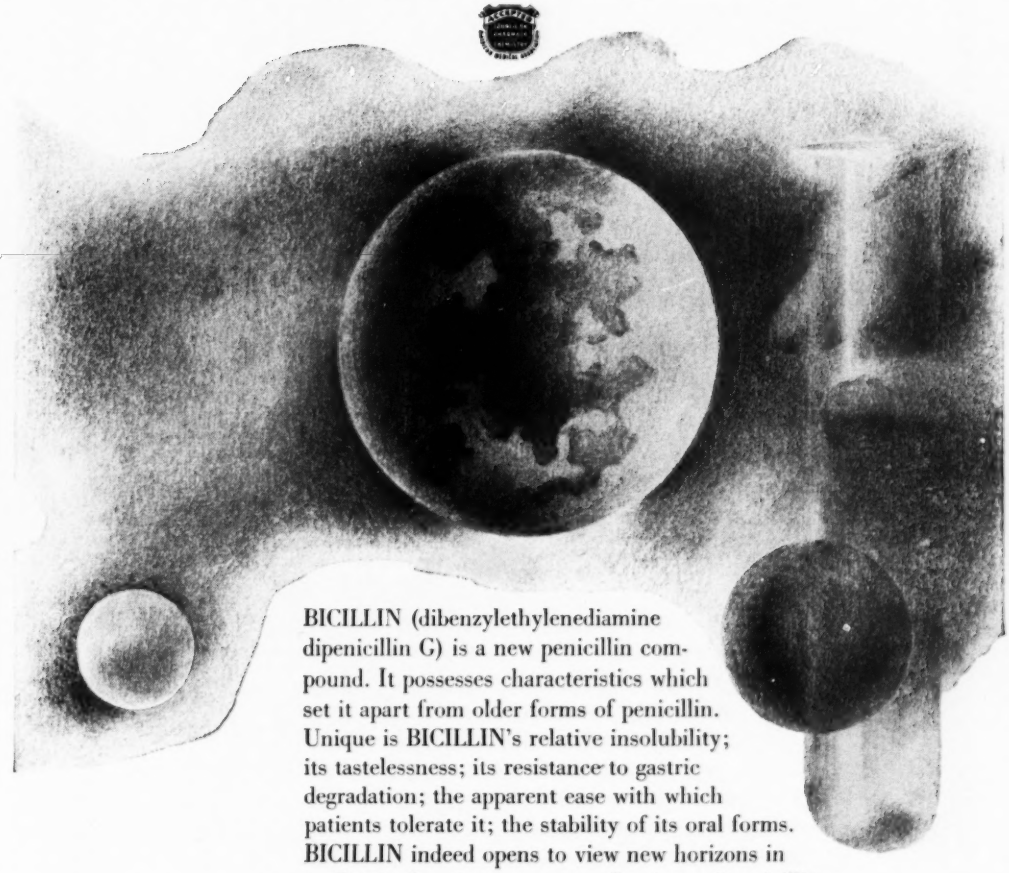
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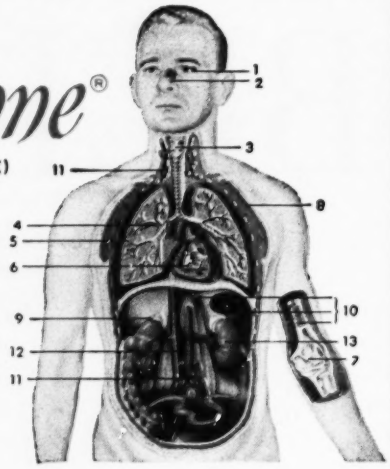
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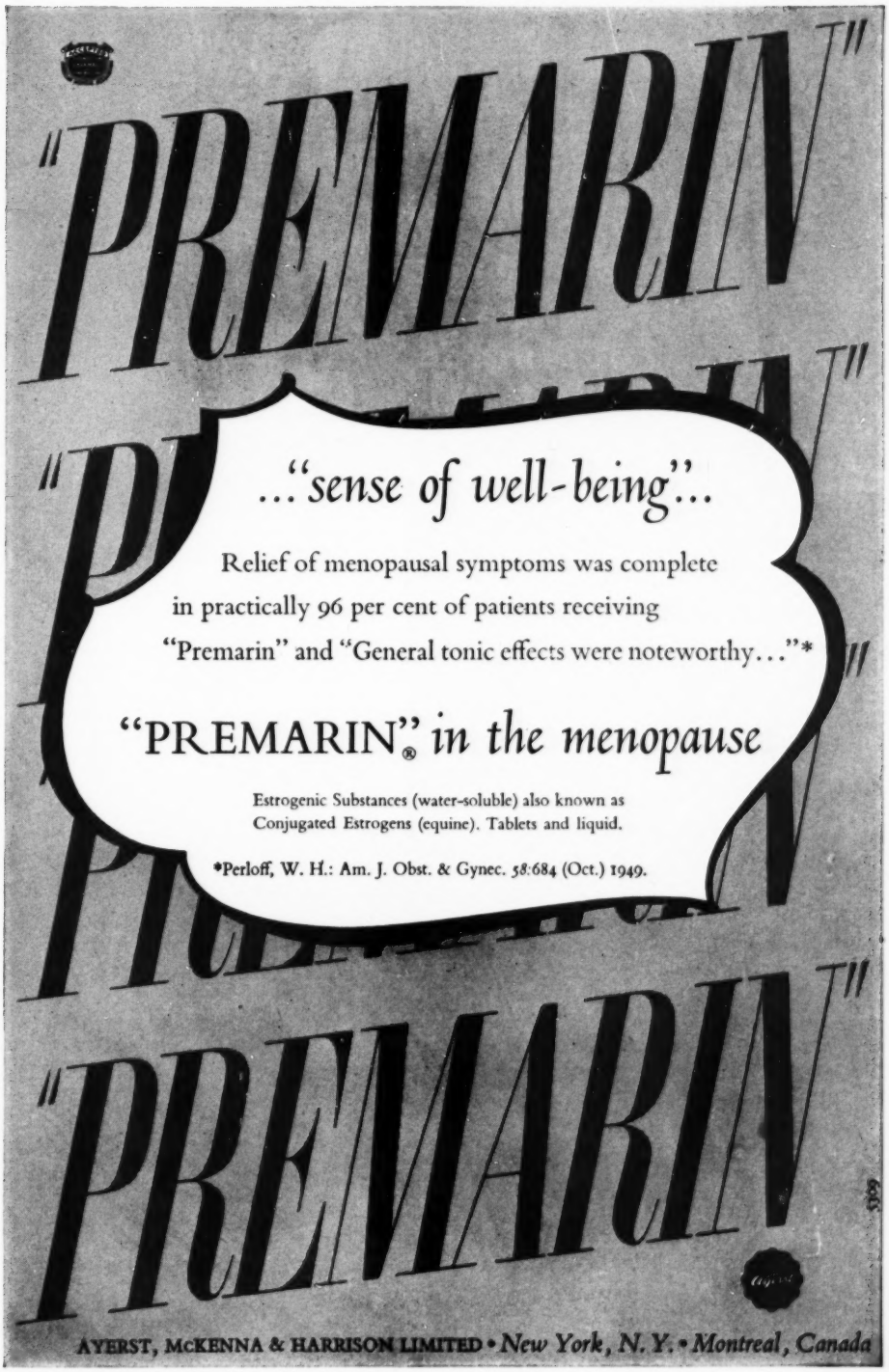
1. EYE—Inflammatory eye disease. **2. NOSE**—Intractable hay fever. **3. LARYNX**—Laryngeal edema (allergic). **4. BRONCHI**—Intractable bronchial asthma. **5. LUNG**—Sarcoidosis. **6. HEART**—Acute rheumatic fever with carditis. **7. BONES, JOINTS, AND BURSAE**—Osteoarthritis; Rheumatoid arthritis; Rheumatoid spondylitis; Acute gouty arthritis; Still's disease; Psoriatic arthritis; Bursitis. **8. SKIN AND CONNECTIVE TISSUE**—Pemphigus; Disseminated lupus erythematosus; Scleroderma (early); Dermatomyositis; Atopic dermatitis; Exfoliative dermatitis; Dermatitis venenata (*e.g.*, poison ivy); Dermatitis medicamentosa. **9. ADRENAL GLAND**—Congenital adrenal hyperplasia; Addison's disease; Following adrenalectomy for hypertension, Cushing's syndrome, and neoplastic diseases. **10. BLOOD, BONE, AND MARROW**—Allergic purpura; Acute leukemia* (lymphocytic or granulocytic); Chronic lymphatic leukemia.* **11. LYMPH NODES**—Lymphosarcoma;* Hodgkin's disease.* **12. ARTERIES AND CONNECTIVE TISSUE**—Periarteritis nodosa (early). **13. KIDNEY**—Nephrotic syndrome, without uremia (to induce withdrawal diuresis). **14. VARIOUS TISSUES**—Angioneurotic edema; Serum sickness; Sarcoidosis; Drug sensitization; Waterhouse-Friderichsen syndrome.

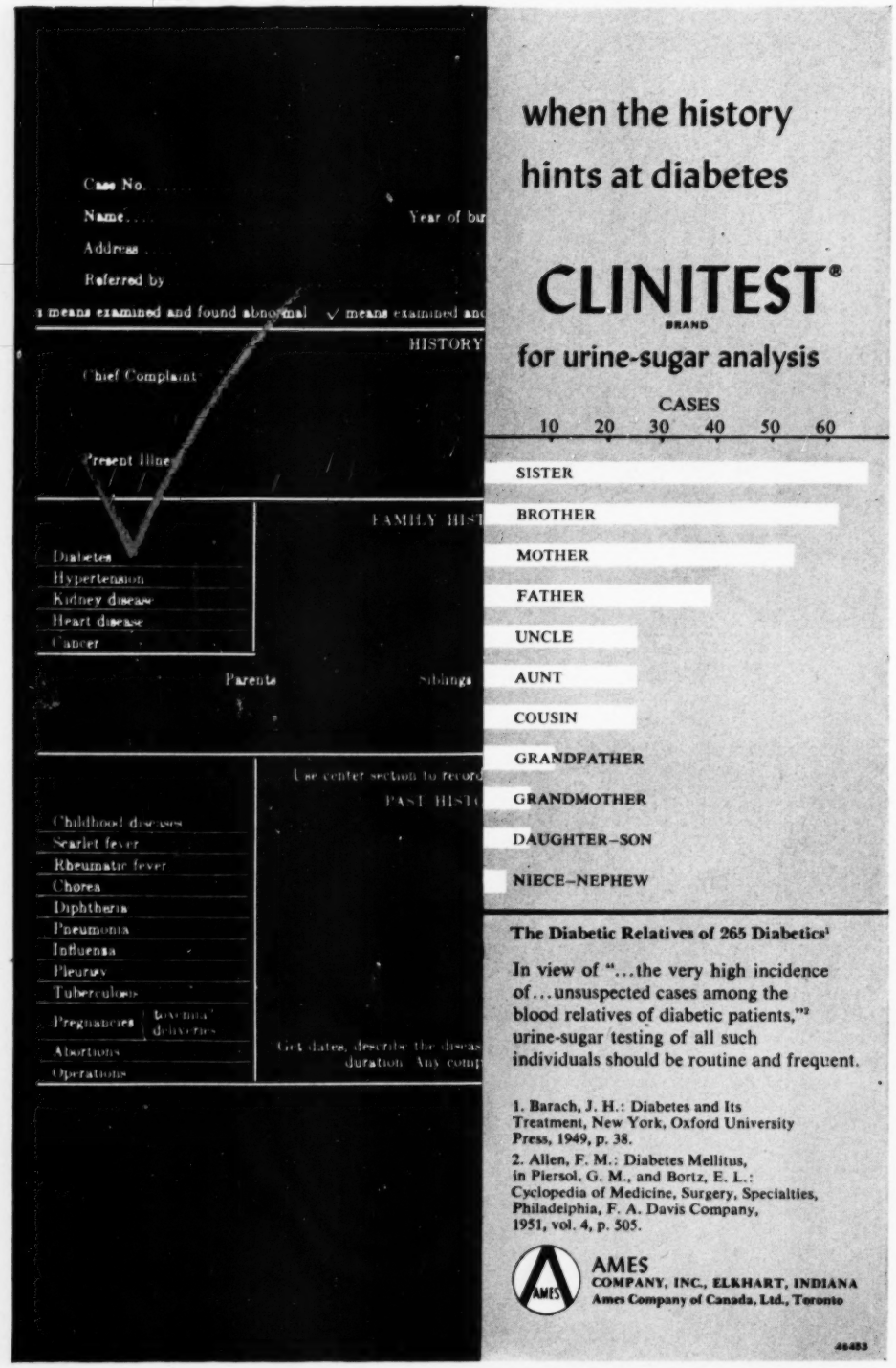
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*Perloff, W. H.: Am. J. Obst. & Gynec. 58:684 (Oct.) 1949.
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1. Barach, J. H.: Diabetes and Its Treatment, New York, Oxford University Press, 1949, p. 38.
2. Allen, F. M.: Diabetes Mellitus, in Piersol, G. M., and Bortz, E. L.: Cyclopedia of Medicine, Surgery, Specialties, Philadelphia, F. A. Davis Company, 1951, vol. 4, p. 505.
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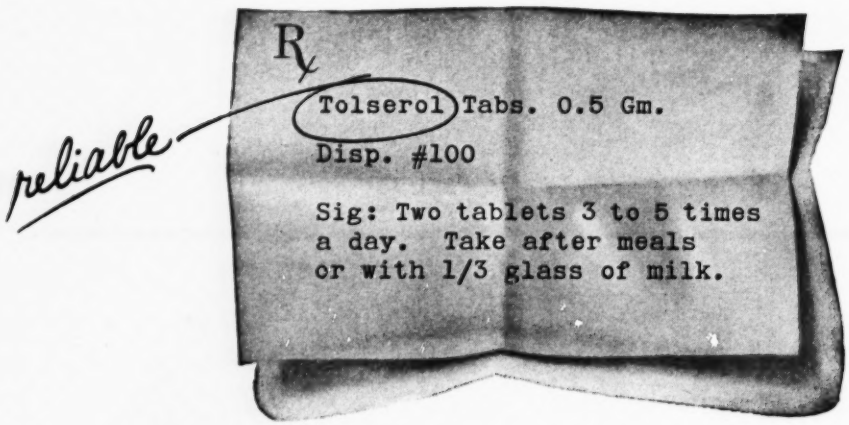
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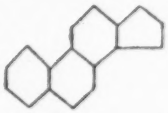
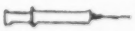
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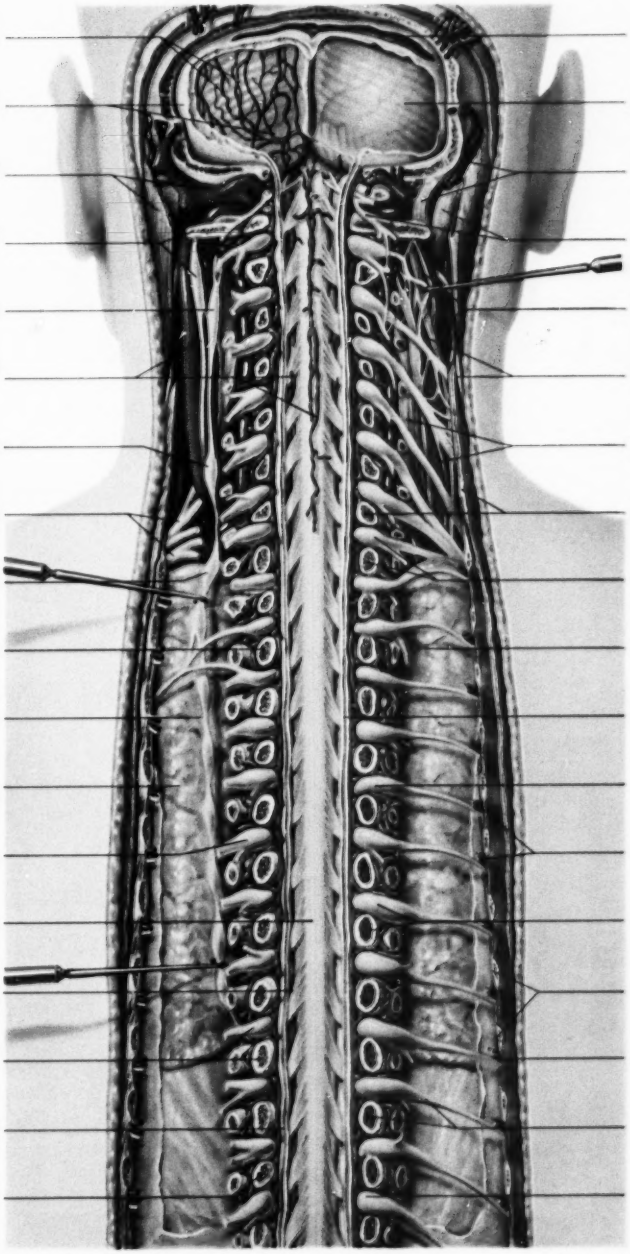


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VOLUME 25
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OCTOBER, 1953

Per Year, $4.00
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TO WHICH OF THESE SHALL WE DIRECT OUR ATTENTION?*

VICTOR D. WASHBURN, M. D.,
Wilmington, Del.

We have been accustomed to thinking of this as a century of progress and achievement in the sciences and in the arts. Organized medicine, in the fields of public health administration, sanitation, medicine and surgery, views with pride and satisfaction the accomplishments of the past fifty years.

To quote Dickinson and Welker[1] "the crude mortality rate of the United States dropped from 17.2 deaths per thousand population in 1900 to only 9.7 in 1949 and an estimated 9.6 in 1950. Spectacular as it is, this drop of almost 45 per cent is in reality an understatement of progress, because the population has doubled, the number of people over 65 has quadrupled." This quotation, brief and limited in scope as it is, may serve to focus attention on the amazing progress that has been made in the conservation of human lives since the beginning of the twentieth century.

These accomplishments may be attributed, in part at least, to the clinical application of knowledge gleaned in the laboratories of countless research workers, the development of immunological and other measures of preventive medicine, the use of antibiotics and chemotherapy, advances in internal medicine, in surgical techniques, in anesthesiology, and in improved living conditions. Credit must also be given to higher standards of undergraduate and postgraduate training which have had an important effect upon the quality of medical care.

As a result of these advances much human suffering has been prevented, the duration of many diseases has been shortened and the lives of countless persons have been prolonged. However, we live in the midst of a changing social order. Nations and peoples are on the march. Old customs and habits are being replaced by others. It is now necessary that we perform our accustomed duties and more.

We are obliged to consider thoughtfully and objectively the criticisms that are directed at us both from within and from without the profession. Where our problems stem from misunderstanding, we must address ourselves to the task of removing the cause of such misunderstanding. If we are at fault, the fault must be recognized and corrected.

Let us consider some of the criticisms and problems as we know them.

It has been stated in the medical press and quoted in the public press that unnecessary operations have been performed. That some surgeons split fees with referring doctors, this without the knowledge of the patients concerned.

Complaints have been made that patients in modest circumstances have been charged beyond their ability to pay, and that some patients are charged exorbitant fees.

We have been told that as doctors we are careless about exercising our right of suffrage, that we do not contribute our share of the cost of operating private community agencies, and that we do not participate in local community organizations.

That newspaper men find doctors difficult, sometimes to the point of irritation and impatience, this because of our unwillingness to speak freely on matters which they consider as of public concern or interest.

The maintenance of good physician-hospital relations with respect to certain of the specialties in medicine is a problem that is nationwide, complex and controversial.

Adequate and competent care for the medically indigent and the indigent represents a major problem not only to the community but the medical profession which should furnish leadership in this field.

* Presidential Address, delivered before the Medical Society of Delaware, Wilmington, October 14, 1953.

The medical care of veterans is a problem that is nationwide, involves everyone, is complex, involved in politics, and the basis for misunderstanding and much ill will toward organized medicine.

Social security for self employed individuals, including physicians, has been recommended to the Congress by President Eisenhower. This too is a subject of controversy which involves the medical profession.

To these criticisms and problems, I have this to offer:

I have been actively associated with the medical profession and the hospitals of Delaware for well over four decades.

I assert that an overwhelming majority of the medical profession is honest and that this applies to all fields of medical and surgical practice. There are those who offend, but these are the exception.

The phrase "unnecessary operation" should not be used carelessly. It is one thing to wantonly perform a surgical operation for the sole purpose of obtaining a fee; it is quite another to operate upon a patient and find that an error has been made either in judgment or in diagnosis.

One of the basic principles of a profession is involved when we discuss such matters as the charge that unnecessary operations are performed, that we split fees, overcharge patients of modest means or other patients.

In Section I of the Principles of Medical Ethics of the American Medical Association[2] it is written: "A profession has for its prime object the service it can render to humanity; reward of financial gain should be a subordinate consideration. The practice of medicine is a profession. In choosing this profession, an individual assumes an obligation to conduct himself in accord with its ideals."

It is important and essential that we realize that it is the duty and the responsibility of each state and local medical society, as well as of each hospital staff, to maintain by example and precept a climate of public medical opinion which will encourage high ethical standards and punish those who fail to conform to such standards.

Frank discussion in advance between doctor and patient of such matters as fees for elective surgical operations, hospital, laboratory and other charges would do much toward improving our relations with the public.

Our Grievance Board must be alert, tactful and impartial, ever ready to listen to those that consider that they have in any manner been treated unjustly by a member of the medical profession.

It is true that as a profession we have, as it were, lived apart. We have been preoccupied at all hours of the day and night with the well-being of our patients. Sometimes our patients have been critically ill and have been entitled to and received our undivided interest and attention. As a profession, we perform many public services.

For example, during the current year, a component of this Society, the New Castle County Medical Society, cooperated with interested citizens in providing leadership in the program which had as its objective the enactment of legislation clarifying the authority of the Wilmington Board of Health.

Another example is that of the Delaware State-wide Chest X-ray Survey, Inc., now in progress. This survey, which is really an extensive, cooperative health education program, was sponsored and supported by public health boards, the Delaware Anti-Tuberculosis Society, the Medical Society of Delaware, the Delaware Division of the American Cancer Society, the Delaware Heart Association, and other private agencies. Members of our Society have devoted many hours to this Survey, making countless addresses to lay groups and attending committee meetings.

We have always devoted a large part of our time and energy to the care of those who are unable to pay for our services. We have been inclined to disapprove of those of our profession who have interests outside of the practice of medicine. In short, we have believed that we had no time to spare for community organizations and that in caring for the poor we had a made substantial contribution and more should not be expected of us. It is my firm conviction, based upon long personal experience, that physicians can

and should broaden their activities. As citizens, they should participate personally and financially in community activities as members of Chambers of Commerce and similar organizations.

They should vote at primaries and elections. Politicians are practical people. They are very much interested in the ideas of people who vote and who are influential in matters of public interest and concern. I hold that physicians can be public-spirited citizens as well.

In Delaware, our relations with press and radio have been, with the rarest of rare exceptions, cordial and cooperative.

The medical profession is deeply indebted to the newspaper profession for its sincere efforts to interpret and convey our messages to the public. Our traditions and those of the newspaper profession stem from the stern experience of many years. Each profession has a duty to the public which is of prime importance. The tradition of the medical man is to be conservative, to emphasize that professional success must come only as the result of recommendations of patients and other members of the profession.

It is within our tradition to conceal from the public matters of controversy until the profession has agreed upon a policy. In our zeal to avoid publicity for those who perform unusual surgical operations or service, we overlook the harm that we do when we, by the pressure of medical public opinion, force anonymity upon those who are designated to act as our spokesman. In this manner, we, in the opinion of the press, sterilize or rob the news of its authority. When we do speak or write, we not infrequently use language which is clear to us, but not to our listeners or readers.

It is in the tradition of the newspaper profession that it is their duty to bring matters of general interest to their readers quickly and correctly. We in the medical profession should realize that we need, indeed we must have, the help of the press as well as that of an informed and understanding public opinion.

Without the assistance of these powerful factors our efforts to control the few recalcitrants within our own ranks will continue to be most difficult, and without avail in our stand against those who would foist socialized medicine upon us. We must know, and be governed accordingly, that the press will be our allies only if our relations with them are based upon frankness and truth. I have had many years experience with newspaper men and women. I have frequently given them, in confidence, information without reservation or evasion. I have never had, at any time, my confidence violated.

The Report of the Joint Committee on Hospital-Physician Relationship of the Boards of Trustees of the American Medical Association and the American Hospital Association has been approved by the House of Delegates of each of these associations. It is an important step forward in that it not only provides a basis for discussion of this exceedingly controversial subject, but also lists six principles which may be used as a guide.

The sixth of these principles reads as follows: "A physician shall not dispose of his professional attainments or services to any hospital, lay body, organization, group, or individual, by whatever name called, or however organized, under terms or conditions which permit exploitation of the patient, the hospital, or the physician." An agreement that no one is to exploit anyone else is a good point of departure. However, it is my opinion that it will take more than this statement of principles to accomplish our purpose.

In order that we might familiarize ourselves with some of the problems and methods of providing medical care for the indigent and the medically indigent, (we consider as medically indigent those who have an income sufficient for ordinary needs, but not for medical expenses) we have invited three of our colleagues from the neighboring states of Maryland and Pennsylvania to describe at this meeting of our Society the methods used by them in attempting to solve this problem.

It is our hope that, as a result of our study of these reports and of those of other states, we may be in a position to recommend to the people of Delaware a plan which would provide a system of good medical care for those who are unable to provide for themselves, including the service of physicians of the pa-

tients' choice on a basis which would not bankrupt the state.

We join with our fellow citizens in the whole-hearted belief that the Federal government has a duty to care for any man or woman who has become physically or mentally handicapped as a result of military service. We are opposed to providing at Federal expense care to Veterans whose disabilities have no relationship to military service.

Our opposition is based upon the fact that we believe that our present policy of providing veterans care for nonservice connected disability will inevitably lead to socialized medicine. We believe that the present program divides our people into those who have had military service and those who have had no such service—the first group to receive medical service provided for out of tax funds and the second group to pay for their own medical care.

We are opposed to the forced extension of "social security" to self-employed individuals, including members of the medical profession. We are opposed because we believe this extension of social security to an additional ten million persons is but another step on the road to socialism—and to socialism we are opposed.

I would answer the question posed in the title of this address in this way:

In the situation in which we find ourselves we must recognize that human relations, public relations, and dynamic leadership are the personal responsibility of each of us who practice medicine.

That this personal responsibility must express itself in the manner in which we deal with individual patients. In our thinking we must consider the financial status of our patients as well as their welfare as citizens, and we must now, as never before, relate our actions to their effect upon the public relations of the medical profession.

That this personal responsibility involves a duty to society in terms beyond our responsibility as physicians and includes activities such as are manifested by public-spirited citizens in other walks of life.

That now we have the opportunity of taking our place with those who would not only preserve and improve the benefits of our system of government, but also oppose those who would weaken or destroy it.

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RENAL UREMIA

Observations On A Series Of 84 Patients With Particular Reference To Combined Electrolyte Management A Preliminary Report*

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Over the past two years certain clinical and chemical observations have been made on 103 patients with renal uremia in Wilmington and Philadelphia. In 84 of these patients a combined electrolyte approach was used as a method of study. This consisted of the administration of hypertonic sodium lactate along with calcium salts and occasionally potassium salts. Since this regime, adhered to strictly, appears to offer a different approach to uremia and acidosis resulting from intrinsic kidney disease, it is the purpose of this paper to relate how such patients are selected for this study, including indications and contra-indications of the regime, along with an exact account of how the electrolytes are administered.

A review of the 84 cases managed will be presented. As the life expectancy of a patient with chronic renal disease in a stable phase of the lesion is unpredictable, the data presented here will refer only to chemical changes encountered in these patients after usual measures failed to produce chemical amelioration. While a certain percentage of these patients showed varying degrees of

*This work was supported by funds made available from the National Heart Institute, Bethesda, Maryland, and the Board of Directors of the Memorial Hospital, Wilmington, Delaware. Subsidiary funds were allocated to this project by the Delaware Heart Association and the Philadelphia Diabetic Society.

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clinical improvement, it must be stressed that the results reported here indicate only a significant fall in the blood urea nitrogen value and an elevation of the CO_2 combining power. More detailed chemical data and clinical results will be the subject matter of future papers. [1, 2, 3]

Case And Methods

Laboratory methodology for the studies will be published in detail elsewhere.[2]

The selection of proper cases for this study is of the utmost importance and will be further discussed under indications and contraindications. The patients selected have been limited to those critically ill suffering from uremia and acidosis due to advanced organic kidney disease. The term "critically ill" is used to include only those for whom routine management seems to have nothing to offer. In the selection of cases a mutual understanding is made with the attending physician that all other available measures of management have been tried without success. The understanding includes that the patient to be studied is in the last stages of the disease. Therefore should the patient die during the period of observation or while receiving specific electrolytes, no discredit or blame may be directed at the regime.

Before institution of the electrolyte study in such cases adequate baseline data should be collected and the following factors must be corrected.

1. **Dehydration** must be treated orally or with intravenous solutions at the discretion of the attending physician. A good urine output is advisable and should there be oliguria due to dehydration, electrolyte management must be withheld until this is overcome. Should clinical improvement result from the correction of this factor or with the other factors to be mentioned, the use of these electrolytes is withheld until an accurate estimation of their need is made.

2. **Infection**: It is known that patients with advanced renal disease are readily susceptible to infection. This may not necessarily be in the urinary tract yet it may lead to a fatal termination. Unfortunately, in patients studied to date, a certain number have failed to react to systemic infections with the usual criteria of fever and leucocytosis. Because of this, comatose patients should perhaps be started upon anti-biotics during the baseline period. Urine cultures should be made during this time as well as other studies that may be indicated in investigating an infection. (Pulmonary and renal infections have accounted for death in several cases, which were not apparent from the clinical or laboratory standpoint.)

3. **Obstruction**: A free flow of urine is necessary and any obstruction in the genitourinary tract must be corrected when possible.

4. **Dietary Protein Restriction**: As part of the usual baseline study in cases that are not comatose, a dietary restriction of protein (20-40 grams daily) with forced calories is urged. This diet also contains one gram of sodium chloride (17-25 mEq). With this diet alone a percentage of cases will show clinical and chemical improvement.[4]

Collection of Baseline Data

No patients except those who are moribund should be exposed to this combined electrolyte approach until adequate baseline data has been collected. At least forty-eight hours baseline data is mandatory and as much as possible must be obtained depending upon individual circumstances (4 to 6 weeks when feasible). The minimum necessary data includes:

a. Blood pressure every four hours times six, then twice daily.

b. A very accurate fluid intake and output on a twenty-four hour basis from 7 a. m. to 7 a. m.

c. Daily weight when possible.

d. Calculation of dietary sodium, potassium and chloride. This may be done by having meals weighed before and after serving and then referring to a standard table.[5]

e. Twenty-four hour urine analysis for sodium, potassium, and chloride. This is absolutely necessary to rule in or out a sodium or potassium losing nephritis.

f. Routine urinalyses done on the first voided specimen daily for three days and then once weekly.

g. Daily blood urea nitrogen and serum

TABLE I

Total Patients Observed	103	Electrolyte Study	84	Response Usual Therapy	5
Expired during baseline period receiving usual therapy	14				

TABLE II

Diagnosis	No. Patients	Chem. Response	No Chem. Resp.	Causes of Failure
Chronic Glomerulonephritis	23	20	3	Progressive Disease Infection Unknown
Chronic Pyelonephritis	19	14	5	All fulminating infections 4 treated less than 72 hrs.
Polycystic Kidney	9	4	5	3 alkalotic from M/6 Na Lactate 1 temporary response 1 infection and cirrhosis
Post-obstructive Uremia	12	10	2	Fulminating Uremia Infection
Kimmelstiel-Wilson's Disease	8	4	4	2 Infection 2 Unexplained
Diabetic Renal vascular disease	2	2	0	Maintenance therapy not necessary
Malignant Hypertension	10	3	7	No clinical response. Chemical only temporary
Senile Nephrosclerosis	1	1	0	
Total	84	58	26	

sodium, potassium, chloride, and CO_2 combining power determinations.

h. Calcium and phosphorus estimation.

i. Sedimentation rate. Infection being ruled out, this associated with increased microscopic or gross hematuria may indicate activity in the kidney lesion, thus presenting a contra-indication to this electrolyte study.

j. Electrocardiogram.

k. Chest x-ray.

l. If edema is present, venous pressure and circulation time.

m. CBC at least weekly.

n. Phenolsulfonephthalein dye excretion.

o. Urea clearance if possible.

PROTOCOL USED FOR THE ADMINISTRATION OF COMBINED ELECTROLYTES:

This protocol must be adhered to strictly in regard to dosage schedule and time intervals.

For simplicity the protocol will be divided into two parts: treatment of comatose cases, and treatment of non-comatose cases. These two will overlap as the management of patients who respond from coma is identical with ambulatory patients excepting early dietary restrictions.

Comatose Cases. All therapy here is intravenous.

1. At 10 a.m. after baseline chemistries have been drawn—assuming dehydration is corrected and a good urinary output is present—1000-1500 cc. of 5% glucose in water or 10% Travert (Baxter's glucose-fructose solution) with two to six grams of calcium gluconate (10% solution)* and ten units of regular insulin. Potassium as potassium acetate or potassium chloride is added to this solution (2 to 4 grams) only if the serum value is normal or low normal and the circulatory system is stable with adequate urine formation. This solution is administered in 2 to 2½ hours.

2. At 4 p.m., never less than three to four hours after the above, intravenously 120-240 cc. of one molar sodium lactate** at times

*A personal communication from Dr. J. P. Peters indicates that intravenous calcium chloride or calcium lactate would probably be more efficacious since the yield of calcium from calcium gluconate is extremely small.

**Eli Lilly preparation of one molar sodium racemic lactate available in 40 cc. ampules used undiluted or when diluted with glucose in water as a ½ molar solution. This was never used in this series in a 1/6 molar concentration.

with equal part of 5% glucose in water. To this is added 0.5 grams aminophyllin and this is given over a period of 1 to 2 hours with frequent check of the blood pressure, pulse and respiration. The amount of sodium lactate used will depend upon a fall in the blood urea nitrogen value, i.e., if an initial drop does not result or continue the sodium lactate is increased. The equal parts of glucose in water are added only if cardiac embarrassment is suspected or if extra fluid is desirable. (Early in the study, certain cases of simple kidney tissue loss received a combination of hypertonic sodium chloride-lactate because of a slow response and a marked decrease in the serum chloride level. This was administered as 200-250 cc. two and one-half percent sodium chloride with 40-120 cc. one molar sodium lactate and 0.5 grams aminophyllin. The effect of this combination was uncertain since there was little change in the serum chloride value.)

At 10 p.m., never less than 3-4 hours after completion of the hypertonic infusion, 1000-1500 cc. of 5% glucose in water or 10% Travert with 2 to 6 grams of calcium gluconate and 10 units of regular insulin should be given. When necessary potassium is added cautiously to this infusion (2-4 grams) depending upon the serum and urine potassium values.

Should the patient rouse from coma with the above management so that water could be tolerated orally the fluid intake is maintained at 2500-3000 cc. (depending upon the urinary output) with supplementary intravenous fluids.

The diet at this point consists of mashed potatoes, salt free toast, and butter with jelly-coke syrup and hard candies. Oral sodium lactate is added as soon as possible and the diet is gradually increased up to 40 grams of protein with 1.0 gram salt.

Non-comatose patients. Since the management of a patient rousing from coma who is able to tolerate oral fluids, food, and medication is essentially the same as the administration of electrolytes to the non-comatose uremic patient the management here is almost identical with few exceptions.

Non-comatose uremic patients are selected for the study if they have a urea clearance of below 5% of normal and a phenolsulfonephthalein excretion of less than 10% total while experiencing symptoms of their disease. These patients are immediately placed upon protein restriction, forced calories, with 1.0 gram sodium chloride daily. The blood urea nitrogen value is followed until it remains unchanged, and then a 10% suspension of calcium lactate in amphojel is begun.[6] Should the serum potassium value be low[7] in such a case a one molar solution of potassium acetate is also started to ascertain the effect of these electrolytes upon the blood urea nitrogen and the CO_2 combining power. When no fall in the blood urea nitrogen occurs or if a falling value becomes stabilized, then one molar sodium lactate is begun. A rising blood urea nitrogen level and a falling CO_2 combining power is an indication for earlier administration of sodium lactate.

The management of the non-comatose patient in regard to electrolytes is as follows:

a. 40 cc. one molar sodium lactate three to five times daily.*

b. 20-40 cc. of 10% suspension calcium lactate in amphojel four times daily.

c. When potassium is needed: 5-10 cc. of one molar potassium acetate 3-4 times daily.**

Potassium values are followed frequently and an upward trend of this value is an indication to stop all added potassium immediately.

If vomiting or diarrhea occurs with institution of oral therapy, the patient is urged to repeat the dose in 20 minutes. Gastrointestinal irritation from the hypertonic solutions tend to disappear in several days.

Anemia is successfully controlled in certain cases with the administration of 100-200 mgm. of cobalt chloride*** daily.[8] If the anemia does not respond within a period of fourteen days and it is felt advisable to attempt to correct the anemia (which is indeed not without danger in the patient with chronic renal disease) the following procedure is

*Special preparation of Robert Bogash, B.S., made available through the Libby Drug Co., Wilmington, Del. This preparation has a high syrup content and furnishes an added 800 calories daily (carbohydrate).
**Also prepared by Robert Bogash, B.S.
***Cobalt chloride prepared by Mr. Robert Bogash, B.S. made available by Libby Drug Company, Wilmington, Del.

adopted. Packed red cells prepared from a fresh donor are obtained within twenty-four hours. Forty cc. of one molar sodium lactate is given intravenously followed immediately by 100-150 cc. packed cells again followed by 40 cc. of one molar sodium lactate. This is repeated every several days until a sufficient response is obtained. To date, with this method, no side effects of transfusions have been noted.

Upon discharge the patient is maintained on the same regime and followed initially at weekly intervals. As an outpatient, determinations are done for blood urea nitrogen, hemoglobin, serum sodium, potassium, chloride, and CO_2 combining power. Each patient is instructed as to recording his own intake and output and weighs himself three times weekly in the morning upon arising. Twenty-four hour urine samples are collected by the patient and brought in for analyses for sodium, potassium, and chloride weekly.

Maintenance therapy has been indicated in most of the cases studied, this being judged by renal function studies below 5-10% of normal or by a clinical and chemical deterioration upon withdrawal of electrolytes.

RESULTS

Table I indicates the total number of patients observed. It is interesting that with salt restriction, protein restriction, forced calories, and the control of infection, dehydration and obstruction, only 5 patients showed a satisfactory chemical response. Fourteen of the patients expired during the baseline period. These constituted cases of chronic glomerulonephritis and chronic pyelonephritis and the reason for exodus was infection or progressive uremia. No favorable chemical results were observed in these cases. Of the 103 patients studied 84 were subjected to a combined electrolyte study.

Table 2 presents data on 84 patients who received hypertonic sodium lactate orally or intravenously along with calcium salts and occasionally potassium. The majority of these patients had adequate control data but early in the study three moribund patients were begun on the regime within less than 24 hours. Thus, it is difficult to evaluate whether or not other measures would have caused a chemical change in these cases. The fall in the blood urea nitrogen and elevation in the CO_2 combining power was significant in 58 of the 84 cases (69%) studied. This occurred after other measures had failed to alter the mentioned chemistries. Certain of these changes were only temporary and this does not imply that permanent chemical amelioration was achieved.

Of the patients studied some improved clinically while others showed only chemical improvement without clinical results. This data will be the subject of future papers.[2, 3]

Any infection may be enough to upset the balance in patients with chronic renal diseases so that uremia and acidosis ensue. This seems to be the most common cause of failure of desirable chemical change in this series. Frequently the infections were not controlled with intensive antibiotic therapy. Several patients with advanced infections with chronic pyelonephritis were treated with electrolyte therapy in an attempt to prolong life until the infection could be resolved. Results were expectedly poor.

It has been of interest that a number of the patients who experienced a favorable chemical change had a reversal of this pattern with discontinuance of therapy. The inexact use of the protocol in regard to dosage schedule and time intervals resulted in poor results in four cases.

DISCUSSION

Since the outlined regime seems to be associated with favorable chemical changes in many patients with uremia and acidosis, it is felt that this presents another method of approach to uremia. In some of these cases the blood urea nitrogen fell as much as 50 mgm % within the first 24 hour period of sodium lactate administration. In certain of the cases the CO_2 combining power rose to above 55 mEq/L but with added calcium no tetany ensued. The fate of the falling blood urea nitrogen level is obscure as present studies indicate that this is not always recovered in the urine.

The serum chloride levels showed a reciprocal drop with the elevated CO_2 combining power, and it is of note that blood lactate

levels as high as 11 mEq/L have been observed in several cases.

Marked uptake of base was seen in many of these patients when electrolytes were administered. This frequently was in the form of sodium, and in spite of significant sodium retention no edema formation was noted; nor was there associated pulmonary edema, induced hypertension or aggravation of an existing hypertension. Eight cases studied lost edema fluid while retaining sodium indicating that the volume of distribution of hypertonic sodium lactate must be greater than the extra-cellular compartment.

Many of these patients were from a large city hospital and follow-up has been lost. Other well controlled cases lived for varying lengths of time on the electrolyte regime. A significant observation on the controlled cases who have eventually come to post mortem examination has been that regardless of the degree or type of kidney disease, sodium may be handled in almost normal fashion when administered as hypertonic sodium lactate. Fox's observations in the nephrotic syndrome[9] as well as our own in this group[10] tend to indicate that this is also true in the stage of subacute nephritis when sodium is administered as lactate or acetate. It appears that the excretion of sodium in advanced renal disease is governed to a large extent by the anion with which it is administered.

Since the clinical usefulness of this therapy is to be established, it is felt that the indications for its use may be found mainly in the following types of kidney disorders—listed in order of best expected response.

INDICATIONS:

1) Post obstructive uremia.

2) Hydronephrosis due to repeated obstructive phenomena as usually associated with prostatic hypertrophy.

Therapy is indicated in these cases only when the obstruction had been relieved and a period of 6 to 8 weeks with adequate fluids and drainage and no chemical or clinical improvement has ensued. Therapy may then be used either to correct the chemistries or as an adjunct to surgical relief.[3].

3) Chronic pyelonephritis.[11] This group of patients should be treated only after repeated urinary cultures are negative and when survival does not appear possible with routine therapy.

4) Diabetic nephrosclerosis. This group may be treated only after regulation of the diabetes and obliteration of any infection.

5) Senile nephrosclerosis. This group may be treated cautiously after the preceding features have failed to benefit the patient.

6) Polycystic kidney disease.

7) Chronic glomerulonephritis. It is felt that patients suffering from this disease who are not moribund should not receive therapy unless the urea clearance and phenolsulfonephthalein repeatedly have been below 10% of normal function.

8) Kimmelstiel Wilson's Disease. This group of patients constitutes a different problem. The regime has been used successfully in such patients, but a 4 to 6 week period of fluid accumulation usually occurs. This is then followed by a gradual diuresis.[12]

CONTRA-INDICATIONS

1) Progressive clinical improvement with routine measures.

2) Any patient with kidney disease not in the chronic stage:

(a) acute glomerulonephritis.

(b) subacute glomerulonephritis with or without the nephrotic syndrome.

(c) chronic renal disease with an exacerbation manifested by an elevated sedimentation rate, increased microscopic or gross hematuria or an active infection of the urinary tract.

3) Tubular necrosis. These patients do not warrant such therapy except under the most unusual circumstances.[13] Potassium particularly must be used judiciously if at all during the phase of anuria.

4) Oliguria. If this is on the basis of a renal lesion and not functional it stands as a contra-indication. In selected cases 2 or 3 days of therapy may be advisable, but should the urine output remain below 300 cc. daily further therapy should not be used.

5) Edema. Edema is frequently a contra-indication. At times, however, the therapy may be used, especially if the patient has edema of Kimmelstiel-Wilson's disease. Ther-

apy may be started and tried for 5 to 7 days in other edematous cases, but if the urine sodium value does not begin to rise or if excessive edema is produced therapy must be stopped.

6) Cardiac Involvement. Since the sodium-retaining effect on the kidney tubules in patients with cardiac involvement is not clearly understood,[14] evidence of cardiac failure whether it be previously due to myocardial or valvular disease or due to a complication of chronic renal disease presents a serious contra-indication. The therapy has been used at times but must be limited only to an investigative nature.

7) Hypertension. Malignant hypertension with renal failure is a definite contra-indication. Hypertension secondary to chronic renal disease is not an absolute contra-indication but satisfactory results may not as frequently be obtained when this feature is present.

8) Cirrhosis. As a complicating feature in patients who also have renal failure, this is considered a contra-indication, since again different mechanisms acting on the kidney tubules are present.[15]

9) Previous Therapy with one sixth molar sodium lactate where clinical alkalosis has already been produced. This is not an absolute contra-indication but makes a good response questionable. At times sodium chloride has been used in conjunction with sodium lactate under these circumstances but with only temporary chemical results.

10) Overwhelming Infection — in patients with advanced kidney disease. This therapy has been tried in this group only in an effort to improve kidney function during an attempt to combat the infection. None of these patients could be included in any series of good results, if improvement resulted.

11) Pathological systemic disease impairing renal function such as multiple myeloma and lupus erythematous.

The major cases of failure of this regime are associated with: (1) Infection. (a) Not recognized ante-mortem. (b) No ability to control infection with anti-biotics. (2) Too lengthy a period of observation since certain cases died with less than 72 hours of electrolyte therapy. (3) Failure to conform to the protocol in regard to dosage and schedule. (4) Activity in the kidney lesion with a clinical picture of fulminating uremia. (5) Several cases showed dramatic clinical and chemical results, but experienced sudden death with no apparent reason for this at post-morten examination. (6) In three instances intravenous sodium lactate was not readily available. Oral sodium lactate was tried but the absorption from the intestines in advanced uremia was dubious since no chemical changes occurred.

The final efficacy of this combined electrolyte regime will ultimately be judged by the reproducibility of clinical and chemical results in the hands of other investigators. Since this approach does produce certain chemical changes, it may perhaps be a contributing point in the management of advanced uremia.

In a review of the literature, it appears the effect of sodium lactate is perhaps different than sodium bicarbonate in control of this uremia, although enthusiastic reports from the use of sodium bicarbonate have been reported sporadically. [16, 17, 18, 19, 20, 21] Recent communications have indicated good results with sodium bicarbonate in uremia in the hands of certain investigators. [22, 23, 24]

The place of lactate in the Kreb's Cycle or the fact that lactate is converted to bicarbonate by a cellular process may be determining features.[25]

It must be stressed that this approach is still investigative in nature, and it should not be attempted indiscriminately unless adequate facilities are available.

SUMMARY

1. A detailed report of the method of administration of certain electrolytes in combination to patients with uremia and acidosis has been presented.

2. The use of this regime was associated with a trend of favorable chemical changes in 69% of the 84 patients so studied.

3. Indications and contra-indications for this study have been presented.

4. Since certain patients benefited clinically as well as chemically after all usual

measures of therapy failed, it is felt that this may represent another approach to the control of uremia.

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MEGALOBLASTIC ANEMIA OF CHILDHOOD

Case Report of a Child Aged 8

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The disease "megaloblastic anemia of infancy" was first recognized as a clinical entity by Zuelzer and Ogden[1] in 1946. Their paper described 25 cases of megaloblastic anemia in infants in which detailed studies had been carried out and included the necessary criteria for such a diagnosis. While it is true that a similarity exists between this disease and pernicious anemia, there is a definite distinction between the two conditions.

Although pernicious anemia of childhood is considered to be a rare disease, many reports concerning it have appeared in the literature, but Peterson and Dunn[2] were the first to set down rigid requirements for such a diagnosis and by inference, question the accuracy of the diagnosis in cases previously reported.[3, 4, 5] The criteria set forth by them and later emphasized by others were as follows: (1) macrocytic anemia; (2) megaloblastic bone marrow; (3) histamine-fast achlorhydria; (4) a therapeutic response to liver or vitamin B_{12} with a relapse when therapy is discontinued. If these criteria are adhered to most of the cases of juvenile pernicious anemia described in the literature become unacceptable, and are best classified as anemias of megaloblastic type

This type of megaloblastic anemia occurs primarily between the ages of 2 to 18 months, and although the etiology is not clearly understood, clinical observations indicate that infection is the precipitating cause, while deficiencies in diet may also cause the syndrome. Thus Zuelzer noted minor infections of ears, bronchi, and intestines as the cause of his patients' illness, but scurvey was also present in 25 per cent of his cases. Similarly, Amato,[6] reporting from Southern Italy, found his patients were fed breast milk for months without supplemental dietary measures.

In the reported cases the patients clinically had fever of varying degree according to the predisposing illness. Splenomegaly was present in less than half the cases, but hepatomegaly was invariably present. Pallor was a predominating feature along with anorexia, nausea, and vomiting. Although histamine resistant achlorhydria was present in most cases, it did not persist after cure of the anemia. The blood picture revealed a leukopenia, but this was not constant and depended upon the initiating infection. Macrocytosis was usually present, but its ab-

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sence did not preclude the diagnosis since the marrow picture was the main diagnostic feature. This marrow picture is described as being identical with that of pernicious anemia in relapse. Hyperbilirubinemia was present in some cases along with an elevated urine urobilinogen, and the platelets were reduced in a majority of cases.

Treatment of this disease is interesting in that unlike pernicious anemia once effective therapy is instituted the condition usually improves never to recur again. Folic acid and vitamin B_{12}[7] are found to be the treatment of choice with folic acid the better agent. Although a chronic deficiency of ascorbic acid seems to precipitate this condition, it is not essential in treatment. Thus, May[8] and his associates produced a megaloblastic type of anemia in monkeys by feeding a milk diet deficient in protein and ascorbic acid. Treatment with ascorbic acid alone did not produce the desired hemopoietic response unless folic acid was added. In humans ascorbic acid by itself is found to be of no value, whereas folic acid with or without Vitamin C will cure the megaloblastic anemia. Thus, we have two drugs capable of rendering a sustained cure, and because of the specificity of folic acid, some feel this disease is purely a folic acid deficiency.[9]

Thus the criteria[10] for a diagnosis of megaloblastic anemia of childhood briefly are: (1) macrocytosis (which need not always be present), (2) megaloblastic type bone marrow, (3) no relapse after therapy.

Zuelzer in his study stated that this syndrome is rare beyond infancy and quotes only one case in a child, aged 5, with celiac disease. The case presented in the present report is unusual since his age far exceeds that usual in cases of megaloblastic anemia of infancy.

CASE REPORT

R. B., aged 8, was admitted to the Memorial Hospital 5/8/53, with a chief complaint of pain in the stomach and fever. The child's history apparently dated back to 5/4/53, at which time he was noted by his physician to have a fever, no other findings were demonstrable at that time. Along with the fever was some nausea, occasional vomiting, and anorexia. The child was given aspirin, but his fever continued to fluctuate between 101 and 99° daily. He was seen again on 5/6/53. At this time nothing further was found except that "his stomach hurt"; there were no findings to account for this fever, so the child was continued on aspirin until 5/8/53. At this time it was noted that the boy had a tender, palpable liver and a palpable spleen, the former extending for 5 cm., and the latter 6 cm. below the costal margin. The child appeared pale, with an icteric tinge to its sclerae, and his skin had a peculiar greenish hue. He was, therefore, admitted to the Memorial Hospital, and on admission it was learned that in the past the child had had a raised temperature about seven months before the admission. He was seen by a doctor at that time and the spleen was palpable. The doctor suspected infectious mononucleosis, but as the boy was not too ill no further studies were done and he apparently made a good recovery. The past history revealed that the child had always been healthy and active and extremely intelligent. He ate well and his mother had no problems concerning his appetite or the amount or the kinds of food he ate. It was also further noted that the child had a normal blood count some years previous at the time of tonsillectomy.

Physical examination revealed a child with an oral temperature of 101, pulse 96, and respirations 16. The skin seemed to have a peculiar pale greenish color to it, and the sclerae seemed icteric. There were some small anterior and posterior cervical nodes, but these were not tender. Heart and lung examination were normal. The liver was palpable and quite tender, extending 5 cm. below the costal margin, and the spleen was also palpable although not tender, extending 6 cm. below the costal margin. The remainder of the examination was normal.

The admission laboratory findings included a red cell count of 2.95 million with 10 grams of hemoglobin. The white count was 3,600 with 55% lymphs, 43% neutrophiles, and 2% eosinophiles, and the urinalysis was normal with the urine urobilinogen positive in a 1:50 dilution. The total bilirubin was 0.9 mgms.% and a bromsulfalein test was 0% while the thymol turbidity was 1.2 units.

Hospital Course: The child continued to spike a temperature between 101 and 98 until 5/27/53, at which time it remained normal.

The child was always very active but his appetite was definitely decreased, and he admitted feeling ill. Laboratory studies which were repeated revealed that the hemoglobin had fallen to 7.25 grams with a red cell count of 2.4 million. The white count was essentially the same. It was at this point that further studies were indicated to determine whether the child had a hemolytic anemia, or whether we were possibly dealing with a hepatitis. Accordingly, a fragility test of the red cells was done which proved completely normal and a Coomb's test was negative. Repeat urine urobilinogens were positive only in a dilution of 1:10. The cephalin flocculation study was 4 plus, and this was repeated 48 hours later and was again 4 plus. The reticulocyte count was 0.3% and this was repeated on three occasions and continued to remain 0.3%. The red cell count fell down to 1.87 million with 6 grams of hemoglobin. A gastric analysis was done on two occasions and free acid was obtained at both times; no histamine was used since the free acid determination revealed 12-20° free hydrochloric acid in the gastric juice. It was at this point that a bone marrow was decided upon. The bone marrow aspiration was done on 5/12/53 and revealed white cell precursors apparently normal. The red cell precursors showed a maturation defect, many megaloblasts being present, the features of the bone marrow being those of a megaloblastic type anemia. Since the reticulocyte counts were low and in the presence of rapidly increasing anemia, it was decided to institute therapy with folic acid and vitamin B_{12}. Because the child appeared ill, it was decided to use both agents together, although it was realized that folic acid alone might suffice. Nevertheless, vitamin B_{12} was given intramuscularly and folic acid in the dosage of 5 mgms. TID were given orally.

On this therapy the child began to improve, and five days after beginning therapy the reticulocyte count rose to 10.6% while the hemoglobin rose to 7.5 grams. A repeat reticulocyte count done three days later showed a 6.1% determination with a hemaglobin of 9 grams. The white count during this time rose to 7,900 with the same differential as presented before. No abnormal cells were ever obtained in buffy coat smears. A repeat bone marrow was attempted on 5/22/53 and at this time the marrow showed a marked hyperplasia of the red cell series, mainly normoblastic in character with only an occasional megaloblast being present. Many of the red cells were polychromatophilic, the features suggesting very active red cell regeneration. The child continued to improve, the liver became less palpable, the temperature remained normal, and by the time of discharge on 5/30/53 the liver was not palpable, although the tip of the spleen was still palpable. The child had lost his peculiar color and was sent home on combined therapy.

As an out-patient he was observed by his physician and monthly blood counts were obtained. His last hemoglobin was recorded as 11 grams with 3.5 million red cells being noted. Physical examination revealed him to be completely normal except for a still palpable spleen, and at the time of writing he has been off therapy for two months. We are anxiously awaiting the results of discontinuing therapy, and routine counts will be taken.

COMMENTS:

This child on admission was thought to have infectious hepatitis but his falling hemaglobin led to further diagnostic measures. Zuelzer records one death in his series in an infant who had a high icterus index and postmortem examination revealed an infectious hepatitis; however, in our patient we did not feel a liver biopsy justified. The anemia could well have been precipitated by a hepatitis, but this is purely supposition and in personal communication[11] other hematologists are of the opinion that the liver and blood picture of our patient could all be on the basis of megaloblastic anemia.

In this case we feel the criteria for the diagnosis were met and the response to therapy is certainly consistent with the diagnosis. The main inconsistent point is the age of the patient as compared to the series in the literature, but cases[12] formerly presented as pernicious anemia in this age group may

well have been megaloblastic type anemias and not true pernicious anemia.

SUMMARY

1. A case of megaloblastic anemia in a child, aged 8, is presented with a good response to folic acid and vitamin B_{12}.

2. Discussion of megaloblastic anemia is presented.

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A CASE OF HEMOCHROMATOSIS (BRONZE DIABETES) IN A FEMALE

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Hemochromatosis, or bronze diabetes, to use its older synonym, is a rare disease of iron metabolism usually seen in males and only rarely in the female. It usually occurs after the age of 50, but in the case to be reported here, which was studied by the authors, the patient was of the comparatively young age of 40 and of the female sex. It is the object of this paper to present this case and also to discuss briefly the disease in general.

CASE REPORT

M. T., Case No. 93191

This 40-year-old white female was first admitted to the Memorial Hospital on 8/21/51 with a chief complaint of abdominal pain. The past medical history included a hysterectomy 28 years previously for unknown reasons; the usual childhood complaints, including chickenpox and measles, and possibly malaria; pneumonia three years prior to the present admission; and two past pregnancies. The patient stated that she had been fairly well until three years prior to admission when she began to notice some bloating after eating followed by some pain located in the mid abdomen. She had never vomited, but had experienced nausea about eight weeks prior to admission. The nausea and pain became worse two months prior to admission, and the abdominal bloating much more pronounced. For two years prior to her admission, she noted a color change in her skin, occurring over most of the body, but especially marked in the hands and the torso. It was less marked in the face, but present there nonetheless. For five years prior to admission she had been treated for a "murmur of the heart" for which she had received digitalis, but she denied taking any silver salts or aspirin. The patient stated that the abdominal pain would usually begin in the mid epigastrium and then become generalized throughout the entire abdomen and was of sufficient intensity to prevent her from sleeping on many occasions. It was described as being of a knife-like stabbing character and, at times, of only short duration. The patient knew of nothing which would relieve the pain.

Physical examination revealed an emaciated, white female who appeared fairly active and alert. The skin of the entire body presented a delicate, slate-gray appearance, discoloration being especially marked in the skin of the hands and of the abdomen. The blood pressure was 90/60; pulse 84; respirations 16 per minute. Examination of the heart showed no enlargement, but a short systolic (grade I) murmur was heard at the apex. Abdominal examination revealed an enlarged, but not nodular, tender liver which extended 9 cm. below the costal margin. The spleen was not palpable. Neurological, pelvic, and rectal examinations revealed no abnormalities.

Laboratory findings showed a red blood count of 3.5 millions, hemoglobin 12 grams, white blood count 3,300 with 7% eosinophiles. A total eosinophile count showed 93 per cubic millimeter, and after the 48 hour ACTH test, the eosinophile count was 44 per cubic millimeter. Prothrombin time was 41%, which on vitamin K therapy increased to 82%. The serology was negative. Urinalysis was negative. BUN was 8 mgms.%, plasma chlorides 615 mgms.%, plasma proteins 7.02 with an

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A/G ratio of 1.3:1. The bromsulfalein test showed 4% retention in 45 minutes; and on the second occasion, 0% in 45 minutes. The cephalin flocculation test was 4 plus, thymol turbidity 6.3 units, total bilirubin 0.9 mgms.%. A fasting blood sugar showed a level of 96 mgms.%, but a glucose tolerance test over a three hour period showed the following levels: 105 mgms.%, 270 mgms.%, 350 mgms.%, 355 mgms.%, and a final reading of 197 mgms. %. Urine sodium showed 20 mEq./L on a 24 hour specimen, and the urinary potassium was 16 mEq./L. An electrocardiogram proved normal, as did a G.I. series and barium enema. Chest x-rays showed pulmonary fibrosis and a small heart shadow.

Further diagnostic tests included a skin biopsy and a liver biopsy. The skin biopsy was reported as follows: "Within the basal cell layer of the epidermis there is a considerable amount of brownish pigment which, by special staining methods, proves negative for iron. This pigment is probably melanin. Scattered in the dermal tissues are a few fine granules of pigment which give a positive iron reaction. This iron is extremely small in amount. Diagnosis—skin biopsy compatible with hemochromatosis." The liver biopsy was reported on as follows: "The biopsy material consists of blood clot together with liver fragments. The liver parenchyma shows marked fatty change, and around the lobules seen in the biopsy material is fairly dense fibrous tissue in which in a few areas there is some bile duct regeneration taking place. Scattered diffusely throughout the tissue, but especially well marked in the liver cells themselves, are brownish granules of pigment. Special staining methods showed this pigmented material to contain iron and it is, therefore, in all probability, hemosiderin. There is no evidence of malignancy. The features here are those of a liver cirrhosis associated with the presence of a large amount of hemosiderin pigment, and they are compatible with a diagnosis of hemochromatosis." Urinary urobilinogens showed values which went as high as a 1:400 dilution. On the basis of all the above findings, it was felt that a diagnosis of hemochromatosis was justified, and after three weeks of hospitalization the patient was discharged to be followed in the out-patient department.

The patient was re-admitted one week after the previous discharge complaining of increased abdominal pain with extreme tenderness in the right upper quadrant and increased abdominal distention. On this admission further inquiry into the patient's history revealed that she was somewhat addicted to alcohol—a fact which had not previously been appreciated. Physical examination revealed the findings already elucidated at her first admission, the only change being an increase in tenderness on palpation of the right upper quadrant of the abdomen. The patient's condition began to deteriorate fairly rapidly, and she gradually passed into a semicomatose state, and it was felt that this was due to hepatic damage. Accordingly, on October 1 cortisone therapy was instituted, the dosage schedule used being that in vogue at that time; namely, 300 mgms. the first 24 hours, followed by 200 mgms. in 24 hours, gradually tapering off to 50 mgms. per day. During the whole of this time she was maintained on continuous intravenous glucose therapy together with the necessary electrolytes required to keep her in a properly balanced state. Seven days following the institution of this therapy the patient began to respond, as evidenced by a lessening of the degree of coma, and a general state of lethargy ensued. Thirteen days after the institution of this therapy the patient emerged from her comatose and lethargic state and became fairly alert and began to take food by mouth. This improvement, however, unfortunately proved to be of a temporary nature only, and she gradually slipped back into a state of coma from which she never recovered, and she expired one month later.

Autopsy revealed the body of an extremely emaciated, while female looking somewhat older than the stated age of 40. The skin over the entire body presented a bluish-gray appearance. The scleroties were yellow in color. The heart was small, weighing 240 grams, but showed no lesions of the valves or muscle. There was no evidence of old or recent infarction. Within the peritoneal cav-

ity adhesions were present between the parietal and visceral peritoneum at many points, especially noticeable beneath the diaphragm. What were described as massive adhesions were present between the omentum and the parietal peritoneum in the region of the umbilicus. The liver was somewhat small, weighing 1,060 grams, and its surface exhibited a marked pebbled appearance with areas of more extensive scarring. The cut surface presented a coarsely mottled appearance, and both the surface of the organ and the cut surfaces were of a uniformly reddish-brown color. The spleen was enlarged, weighing 320 grams. Apart from a large infaret, the splenic parenchyma appeared normal. The pancreas was of firm consistency and had a reddish-brown color, and the gross examination showed an apparent increase in the amount of fibrous tissue in the organ. The veins at the esophagealgastriet junction were much more prominent than in a normal subject and were apparently varicose. The remainder of the gastrointestinal tract appeared to be normal. The body of the uterus was absent, but the cervix remained. The left ovary was absent; the right ovary was present, but appeared normal. The lymph nodes alongside the abdominal aorta were enlarged, soft in texture, and presented a reddish-brown color. The remainder of the organs appeared normal to gross examination.

Histological examination showed the following features: The liver showed advanced fatty change of the liver cells together with a marked multilobular cirrhosis. In the areas of fibrosis there were collections of lymphocytes and areas of bile duct reduplication. Within the liver cells and also within the fibrous tissue there were large deposits of hemosiderin. The pancreas showed a marked increase in the interstitial tissue of the organ, lying in which the glandular elements were forming small clumps. Both within the fibrous interstitial tissue and in the cytoplasm of the cells forming the parenchyma of the pancreas there were deposits of hemosiderin granules. Similar granules were present in the cytoplasm of the islet cells. The musele fibers of the myocardium showed granules of hemosiderin lying on either side of the nuclei. The abdominal lymph nodes showed deposition of hemosiderin within the reeticuloendothelial cells of the tissue. The pituitary gland showed deposits of hemosiderin lying within the cytoplasm of the cells making up the anterior part of the gland. Similar deposits of hemosiderin were noted in the cells of the ileal mucous membrane and in the cells of the zona glomerulosa of the adrenal glands. Similarly, the cells of the gastric mucosa showed deposits of hemosiderin. The lungs showed a well marked bronchopneumonia, and the spleen showed an area of infarction, but no hemosiderin was noted in this organ.

DISCUSSION

Hemochromatosis is a disease characterized by the following triad of symptoms: pigmentation of the skin, cirrhosis of the liver, and diabetes. It is a comparatively rare disease, being more common in males than females, and up to the year 1950, only thirteen cases had been recorded in the latter. It is a disease of later life, the majority of cases occurring after the age of 50 and no case has been described in a patient below the age of 20 years. It has been suggested that the age incidence is due to the fact that a long period of time is needed for the deposition of the excess iron, and the sex distribution by the continued monthly loss of iron in the female over a considerable part of her lifetime, thus giving less opportunity for excess iron accumulation. As mentioned previously, the case described here is of unusual interest in that the patient was a female of the comparatively young age of 40 years.

In the past, diagnosis has rested on clinical findings, diabetes as indicated by laboratory tests, and the somewhat unreliable method of skin biopsy. With the introduction of liver biopsy, however, a most useful diagnostic technic is now available,[2] since the histological picture of the liver in this disease is almost pathognomonic.

Desforges[3] has drawn attention to the fact that abdominal pain may be a major symptom in patients suffering from hemochromatosis, and it is interesting that this symptom was so prominent in the patient presented here. One of the theories advanced for this pain

is that it is due to adrenal cortical insufficiency, and while it is true that there was histological evidence of adrenal involvement in the present case, it must nevertheless be recognized that this patient also had rather extensive intraperitoneal adhesions which, although unlikely to have caused her type of pain, might conceivably have done so.

The etiology of this disease remains obscure. Some years ago Mallory's theory of copper intoxication based on animal experiments proved popular, but this has now been generally discarded. It would seem that in some way the intracellular iron physiology is upset, but this is mere speculation. Attempts to produce hemochromatosis in animals by continuous intravenous administration of iron have proved inconclusive, but it is significant that in recent years cases of hemochromatosis have occurred in patients who have received multiple blood transfusions over a period of years.[4]

SUMMARY

1. A case of hemochromatosis in a comparatively young female is presented.

2. A brief discussion of the disease is presented.

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A METHOD OF TREATMENT OF STASIS ULCERS OF THE LOWER EXTREMITY

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The method of treating stasis ulcers of the lower extremity to be herein described is composed of the old method, (apparently largely forgotten with the passage of time), of applying pressure with a rubber sponge and elastic bandage, combined with the use of Varidase (streptokinase and streptodornase, Lederle) ointment.

The application of pressure by means of a rubber sponge was described by McPheeters in 1929 and before him in 1924 by Nobl. The method used by the present author is essentially similar to that described by McPheeters, with a few modifications, and is as follows:

The ulcer area is cleaned with a 1:1000 solution of aqueous zephiran chloride, the necrotic tissue is debrided away, and any exuberant granulations are cauterized with a silver nitrate stick. A bland ointment is then applied to a piece of sterile gauze, and the gauze is applied to the ulcer. Bacitracin ointment has been found to be ideal for this purpose, because it speedily clears up infection; it is a non-greasy ointment and is therefore easy to remove at the time of redressing, in contrast to zinc oxide ointment, for instance, which is difficult to remove; and it prevents the gauze from adhering to the ulcer. Several layers of gauze are placed over this to absorb the ulcer exudate, and next a piece of foam rubber, one-half to one inch thick, which will cover an inch or more beyond the edge of the ulcer is applied. Several more layers of gauze are applied over this, and the whole is snugly wrapped with a two or three inch cotton gauze bandage. An Ace elastic bandage is then wrapped on the leg from the toes to the knee. If an ordinary cotton elastic bandage is used, it should be applied as tightly as possible, but if a rubberized elastic bandage is used, and this type is somewhat better because it more satisfactorily conforms to the contour of the foot and leg, one should be very careful not to draw this too tightly, because it is possible to produce ischemia and gangrene with a rubberized bandage. An elastic bandage does not usually remain satisfactorily wrapped for more than a day or two, so it can be removed and rewrapped by the patient or physician as necessary, without disturbing the dressing beneath, which is held in place by the gauze bandage. The whole dressing should be changed when necessary and this is usually every other day to twice a week at first, but as the ulcer becomes cleaner and the exudate diminishes, once a week may be sufficient. Further debridement should be done at each redressing.

It is important to have the patient carry on his usual activities during the treatment,

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and he should be told that the more he walks, the quicker the ulcer will heal, as the muscular action involved helps to improve the sluggish circulation and hasten the subsidence of the edema. If the patient walks enough, the pain from the ulcer is usually gone in several hours after the first application of the dressing.

When the ulcer has become free of necrotic tissue, edema and inflammation have subsided, and it is covered with healthy granulation tissue, usually a period of two to four weeks, it is time for epithelization to take place. The rubber sponge pressure treatment is continued, but instead of bacitracin ointment, Varidase ointment is used and redressing is carried out twice a week. The rapidity with which epithelization will take place under the influence of Varidase ointment is phenomenal. In one week the ulcer is often half covered with epithelium and within two weeks it may be completely healed. This of course depends on the size of the original ulcer. After treating my first case with this ointment, I could not believe that any preparation could cause such rapid healing. But after several more were treated with the same results, I became convinced that the Varidase ointment has some property which directly or indirectly stimulates rapid epithelization.

Varidase ointment is prepared in the following way. One vial of Varidase powder and 300 mg. of aureomycin powder are thoroughly mixed in about 5 gm. of lubricating jelly (Lubafax is the particular one used, although any brand would presumably be just as good). This ointment is stable for about two weeks if kept refrigerated, in contrast to water solutions of Varidase, which are stable for only a few hours.

When the ulcer is healed, appropriate measures to treat the underlying cause should be carried out. Varicose veins are the chief cause, but in some cases of long standing varices with trophic skin changes, or in cases of the post-phlebitic syndrome with edema, the patient may have to wear elastic bandages or elastic stockings permanently.

ETIOLOGY OF STASIS ULCERS

It is generally agreed that stasis ulcers are caused by a sluggish, static, or actually reversed venous blood flow in patients with varices. These changes in blood flow result in local anoxia and tissue edema, which in turn cause impairment of nutrition locally and a decreased resistance to trauma and infection. Patients frequently give a history of a minor trauma to the affected part, with the subsequent development of an ulcer. These ulcers are a type of trophic ulcer and in early cases they may be healed without any permanent damage to the skin or subcutaneous tissues. However, in more advanced cases of varices, or in the post-phlebitic syndrome, there are permanent changes consisting of pigmentation and thinning of the skin and induration and scarring of the subcutaneous tissues. There are also some trophic ulcers, i.e. ulcers with these same changes, which defy classification because there is no history or sign of varices and no history or evidence of phlebitis. Two such cases are included in the case reports to follow.

It should be emphasized that there are ulcers having an appearance similar or identical to stasis ulcers, but which are of different origin. These include luetic, tuberculous and mycotic ulcers, and ulcers caused by deficiency in arterial circulation. Occasionally malignant ulcers may stimulate stasis ulcers. Any of these types require treatment of the primary etiology before they can be cured and one must rule out these types before beginning the therapy as herein described.

RATIONALE OF THERAPY

In order successfully to treat stasis ulcers, one must have a method which will at least partially reverse the pathologic changes. It is evident that the pressure method described will eliminate edema and correct the static or reversed blood flow. An elastic bandage alone will do this to some extent, but the addition of the rubber sponge produces a greater and more uniform pressure in the area of the ulcer.

As soon as the edema is gone and blood flow corrected, the skin will improve in appearance and texture; the ulcer, which was formerly deep, will now be shallow due to the subsidence of edema; and the ulcer base will be-

come covered with healthy granulations under the influence of debridement and bacitracin.

The addition of Varidase ointment at this point will cause rapid epithelization of the ulcer. The exact mechanism for this is not clear, but it is known that the Varidase dissolves the exudate and thereby permits more effective action of the locally applied antibiotic (aureomycin), no longer hindered in its pursuit of bacteria by a thick, impervious exudate. It is thought by some that Varidase in some way stimulates epithelization, and indeed it seems so, but this has not been proven. The importance of Varidase, however, in healing an ulcer, after the initial improvement with the pressure treatment, is brought out in the case reports. It must be emphasized that Varidase will dissolve only exudate, and not necrotic tissue, so it is no substitute for mechanical debridement. I have seen several ulcers vainly treated with Varidase when debridement was neglected, with considerable loss of time and energy, not to mention financial loss to the patient.

A final emphasis should be placed on the fact that some cases of post-phlebitic syndrome, with occlusion of the deep venous circulation, will not tolerate elastic bandages, because they occlude the only remaining circulation, which is through the superficial veins. Fortunately, I have not encountered such a patient with an ulcer, else he might have had to keep his ulcer, but I have encountered one such patient who did not have an ulcer.

One may question what advantages, if any, this method of treatment has over the use of the Unna paste boot. The latter method is indeed an effective one, but I believe it has its disadvantages. In the first place the process of applying an Unna boot is messy and time consuming, whereas the rubber sponge method is relatively quick and easy. Secondly, the Unna boot is usually left in place for one to three weeks and I doubt if the resultant continual bathing of the ulcer in its own infected exudate is as good for the ulcer as bi-weekly cleansing and debridement. Thirdly, the Unna boot has to be applied with particular attention paid to absolutely even wrapping of the bandage, else a small wrinkle may produce a new ulcer. I have seen such a case. (See Case reports).

The following three case reports are representative of the ulcers so far treated. A total of seven have been treated in the past two years, with uniformly good results.

Case 1. The patient, A. G., a 59 year old white female, had varicose veins of both legs of long standing and a bilateral post-phlebitic syndrome. Both lower legs were edematous, there were trophic skin changes, and the subcutaneous tissues were indurated. The legs were painful and the patient wore elastic bandages whenever she was on her feet. The varices were not evident except in the upper portions of the great saphenous veins, because the legs were obese and edematous. She had previously had a left high saphenous ligation with little improvement. On October 23, 1950, she had a right high saphenous ligation because of three ulcers on her right ankle. Post-operatively she was treated in the clinic twice weekly with application of various ointments and rewrapping with elastic bandages. Under this treatment two of the ulcers healed, but the third remained stationary. In March 1951, an Unna paste boot was applied and on removal three weeks later there was only slight improvement. She was again treated with elastic bandages and ointments until August 1951, with no improvement, at which time a modification of the Unna boot was applied, known as Gelocast, which is an elastic, adhesive bandage impregnated with chemicals similar to those used in an Unna boot.

On September 8, 1951 this boot was removed and the patient was seen by author for the first time. The old ulcer was healed, but there were four new ones over the back of the right ankle, resulting apparently from wrinkles in the Gelocast bandage. On September 15, 1951 the McPheeters rubber sponge pressure method was begun and in two months two of the ulcers were healed. The remaining two, the larger of which measured 3x2 cm., were shallow and covered with healthy granulations, but exhibited no tendency to epithelize. Varidase ointment was added to the treatment on November 16, 1951 and dressings were changed twice a week.

Healing was remarkably rapid and on November 30, two weeks later, both ulcers were completely epithelized.

Because of improper care by the patient and resistance to follow-up, the patient developed a recurrent ulcer twice and both times healing was satisfactory with the same treatment. At this writing she is undergoing treatment for another ulcer, this time on her left ankle.

Case 2. This patient, M. L., was a 64 year old white female admitted to the hospital on October 13, 1951, with a history of a recurrent ulcer on the medial aspect of the left ankle for twelve years, and on the right ankle for one and one-half years. Both ulcers had been present constantly since April 1951. The ulcers had been successfully treated many times, but had always recurred. There was no evidence of varices and no history of phlebitis or signs thereof. Serology was negative, fungus culture negative, culture for bacteria showed staphylococcus albus, and biopsy from one of the ulcers showed only a chronic skin ulcer. A feasting blood sugar was normal. The only systemic disease noted was a rather severe rheumatoid arthritis.

On the medial side of the right ankle was a shallow 4x2 cm. ulcer and on the left an ulcer measuring 6x3 cm. They were foul smelling had a necrotic base and a purulent exudate. The borders were irregular, indurated and reddened and there was slight edema of the ankles.

The patient was treated with warm compresses of 1:1000 aqueous zephiran chloride locally and penicillin systematically. The ulcers became clean and covered with healthy granulations, but no epithelization took place. On October 26, 1951 daily applications of Varidase ointment were begun, but no pressure dressings. In six days 50% of the ulcer surfaces were epithelized. The patient was discharged from the hospital on November 3, 1951 and instructed to apply the varidase daily herself. Further improvement was slow, so the rubber sponge pressure dressings were added on November 24, 1951. On December 8, 1951 the left leg was healed and on December 15, 1951 the ulcer on the right leg showed complete epithelization.

This patient has had no recurrence of her ulcers since that time and she keeps both legs wrapped with elastic bandages whenever she is on her feet.

Case 3. The patient, C. S., a white male, aged 70, had a history of a recurrent ulcer over the left medial malleolus since 1934. In August 1952 the ulcer was excised and a split thickness skin graft was applied. The graft sloughed out completely and the ulcer failed to heal.

He was readmitted April 2, 1953, at which time he had three partially confluent ulcers over the left medial malleolus, the largest measuring 5x2.5 cm. There was a one plus ankle edema, redness and induration around the borders, necrotic tissue at the base and a purulent exudate. The left lower leg showed trophic skin changes. There was no history or evidence of varices or phlebitis. Serology was negative and there was no diabetes.

Treatment with warm compresses of 1:1000 aqueous zephiran produced little improvement, nor did the use of a cod liver oil ointment.

On April 14, 1953 and April 16, 1953 the ulcers were dressed with bacitracin ointment and the rubber sponge pressure dressing with elastic bandage. On April 17, 1953 the edema was gone and the ulcers were clean. Varidase ointment was added to the pressure dressings and redressings were done every other day. In twelve days complete epithelization had taken place except for a small area measuring 4x2 cm. He was discharged on April 29, 1953, continuing the same treatment as an out-patient, and in two weeks healing was complete. There has been no recurrence.

This case represents a trophic ulcer with no ascertainable cause, such as varices or phlebitis, as does Case 2.

SUMMARY

1. A method of treating stasis ulcers of the lower extremities is presented which combines the McPheeters method of a rubber sponge pressure dressing and elastic bandage, with the use of bacitracin ointment to control infection, followed by Varidase ointment to promote epithelization.

2. The etiology of these ulcers is based upon a static or reversed venous blood flow

with resultant ischemia and edema which lead to impaired nutrition locally and decreased resistance to trauma and infection.

3. The rationale of this therapy and the advantages of their method over the use of the Unna paste boot and of bed rest are discussed.

4. Three illustrative case reports are presented.

5. Seven cases have been treated in the past two years by the method described, with uniformly good results.

6. It is believed that this method of treating stasis ulcers of the lower extremities, if carefully followed, will give us good, and probably better results than any other method yet devised.

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CHONDROSARCOMA
A Case Report

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A case of chondrosarcoma arising from the 9th costochondral junction was observed and treated recently at the Memorial Hospital. It is reported because of the comparative rarity of these tumors and the interesting diagnostic possibilities entertained in this case.

N. T., a 63-year-old colored male, was admitted to the Memorial Hospital on 1/26/53. He had been under treatment since June, 1951, for hypertensive cardiovascular disease complicated by hypertensive neuroretinopathy and bilateral cataracts. The original record at the time of his first examination made note of a bony prominence present over his right 9th rib and attributed it to an old fracture at that site. The patient stated he had had a fracture of a rib in that area in 1939, but had not noticed any superficial lesion until 1949 when a small nodule appeared which slowly and progressively enlarged to its present size. In the month prior to admission the patient felt the tumor had enlarged more rapidly. The precipitating reason for his admission to the hospital was a terminal stream hematuria of three weeks' duration associated with dysuria, urgency and nocturia.

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The past history was significant for known Neisserian infections in 1920 and 1930, and a fracture of the right 9th rib in 1939.

Physical examination revealed a middle-aged, well-developed colored male in no apparent distress.

Except for biliteral lenticular opacities and poor dental hygiene the head and neck examination was negative.

Examination of the chest revealed an old healed transverse scar overlying the left 6th rib, the result of a knife wound and a firm, non-tender tumor measuring 6 x 6 x 5 cm. overlying the right 9th costochondral junction. The skin was intact and easily movable over the tumor which was firmly fixed to the underlying structures.

Th heart borders were enlarged to percussion and an auricular fibrillation was present. The lungs were clear to auscultation.

A grade I prostatic enlargement was present but both lobes were smooth and compressible and the median furrow was present.

The remainder of the examination was negative. There was no palpable peripheral adenopathy.

Cystoscopy was done on 1/26/53 and except for a stricture encountered in the posterior urethra no lesion could be demonstrated. Retrograde pyelography revealed renal pelves normal in outline. Deviation of the midportion of the right ureter medially, prompted speculation on the possibility that a tumor of the lower pole of the right kidney might be responsible, but after a liquid diet for 48 hours a scout film of the abdomen revealed normal kidney outlines, bilaterally.

Roentgen examination of the chest on 1/27/53 revealed. . . . "a large tumor mass in the right anterolateral chest wall. There is some pathologic involvement of the anterior end of the right 9th rib and a fracture is present. This large mass has caused very little rib destruction at the present time and is probably invading the rib by contiguity . . . there are no metastatic lesions in the lung fields."

A skeletal survey was carried out and the following information obtained: "The lumbar spine shows no abnormality. Severe arterial sclerosis of the abdominal aorta and iliac vessels is present . . . the dorsal spine is intact. The shoulder girdles show no

change . . . there is periosteal change in the lower third of the femur . . . there is a calcification in the muscles of the middle third of the right thigh . . . there is a peculiar lesion in the lower end of the left tibia. This should be re-examined by spot-films . . . re-examination reveals changes in the left ankle that seem to be the result of an old injury. Considerable traumatic arthritis is present in the ankle joint and periosteal bone proliferation has occurred in the tibia . . . there is a shadow in the lateral projection of the sella turcica which may indicate sclerosis of the internal carotid artery at the level of the carotid siphon."

Chemistries obtained at this time were as follows: RBC 4.6; Hb 12.0; WBC 7,650 with 75% polymorphonuclears.

Urinalysis: pH5; S. G. 1.014; Alb. 2+; sugar, negative; RBC, solid field; alkaline phosphatase 3.2, B. U. N. 15, calcium 9.0, phosphorus 3.3. Total proteins 7.56. A/G ratio 1.6 — 1.0.

An electrocardiogram revealed a marked left ventricular preponderance and confirmed the auricular fibrillation.

An aspiration biopsy of the mass on the right anterolateral chest wall was reported as having "only cartilagenous material present . . . no malignant cells are seen."

With the apparent exclusion of the possibility that the tumor of the chest wall was metastatic in origin and the disappearance of the hematuria after dilatation of the urethral stricture, it was decided to treat the chest wall tumor as a primary tumor of the underlying bone or cartilage. Surgical treatment was advised and accepted. Medical consultation was obtained regarding the patient's operability and it was their opinion that any prolonged extensive procedure was contraindicated in view of his relatively poor cardiovascular status. Accordingly, the patient was prepared for surgery.

On 2/11/53, under endotracheal anesthesia, the 9th rib was initially divided in the right mid-axillary line and after incision of the pleura, examination of the pleural cavity was carried out. No metastatic disease was seen or palpated in the adjacent diaphragm, hilus of the lung, etc., but a bulging of the pleura beneath the 9th and 10th ribs was palpated which was not appreciated preoperatively. The intrapleural tumor mass measured 3 x 2 x 2 cm. Accordingly, a block removal of the tumor mass was carried out extending from the mid-axillary line to the costal margin including a wide margin of skin, fat, muscle, pleura and the 9th and 10th ribs with their cartilagenous portions anteriorly. Except for undercutting and approximation of the skin margins, no further measures were considered necessary to close this defect of the lower chest wall.

Examination of the specimen postoperatively revealed a glistening, friable, almost crumbly mass of tumor encased by a definite capsule anteriorly with the skin freely moveable over it. Invasion of the ribs had occurred with the tumor eroding through the ribs and bulging the underlying pleura.

Microscopic examination "shows the tumor to be made up of atypical cartilage calls lying in a hyaline type of matrix. The tumor is fairly well differentiated . . . chondrosarcoma."

The patient's postoperative course was satisfactory and he was discharged on the 12th postoperative day.

It is appreciated that the treatment of choice is the complete removal of the ribs involved plus one or two above and below those involved. However, the patient was considered a poor operative risk and this restricted any procedure more extensive than the one accomplished.

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ERYTHROMYCIN IN THE TREATMENT OF PNEUMOCOCCAL PNEUMONIA

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Erythromycin** is an antibiotic produced by certain strains of *Streptomyces erythreus* and is described by McGuire and others.[1] It is administered only by the oral route and except for nausea, vomiting or diarrhea, there

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**Erythromycin used in this study was generously provided to us by the Lilly Research Laboratories through the courtesy of Dr. J. W. Smith. The trade name adopted for this antibiotic by Eli Lilly and Co. is "Ilotycin."

have been no reports of toxicity.[2] There is laboratory and clinical evidence that it is effective in infections caused by many gram positive bacteria, including hemolytic streptococcus, *Staphylococcus aureus*, and pneumococcus.[1, 2, 3, 4]

Pneumococci have been demonstrated *in vitro* to be sensitive to erythromycin in concentrations from 0.009 to 0.09 micrograms of erythromycin per milliliter. Haight and Finland[3] tested 58 strains and found minimum complete inhibitory concentrations for two-thirds of the strains to be 0.04 micrograms per milliliter.

Therapeutic blood levels in concentrations of one to twenty micrograms of erythromycin per milliliter have been demonstrated,[2, 4] and there is a rough correlation between the maximum blood level and the dose. A peak is reached between one and two hours with a rapid decline between the fourth and sixth hours.[4] Simultaneous administration of sodium bicarbonate does not affect absorption.[4] Erythromycin is rapidly destroyed in an acid media. By using tablets coated with an acid-resistant alkali-soluble material, a slower but higher blood level is usually reached, even in the non-fasting person.[2]

Smith and others[2] treated 8 cases of lobar pneumonia and isolated a pneumococcus from the sputum of 7 cases. Four of these cases also had pneumococcal bacteremia. Dosage employed was 300 mgs. or 500 mgs. every 6-8 hours. Six cases showed a rapid favorable response although a slow resolution of the pneumonic process occurred in 3 cases. A secondary infection with *Klebsiella pneumoniae* occurred in the remaining two cases, one of which expired. Treatment with another antibiotic was necessary for this complication.

Haight and Finland[3] treated 41 patients, including 15 cases of pneumococcal lobar pneumonia. There were 4 cases with bacteremia, two of which expired. One case had a massive hemorrhage from a gastric ulcer and the other case, after being acutely ill for two weeks, died on the second day of therapy. The 11 non-bacteremic patients showed a rapid favorable course, with subsidence of fever and symptoms in twenty-four hours. Pneumococci were absent from the sputum in all cases by the third day, and no specific organism replaced the pneumococci in the sputum. Dosage schedules were varied and most of the cases received 5 to 8 gm. in 4-8 days.

Haight and Finland[3] state that the clinical effects of erythromycin in the 16 cases were essentially similar to those observed with sulfadiazine, penicillin, or the broad spectrum antibiotics. Although erythromycin has been used in relatively few cases, Smith[2] says that it is at least moderately effective in the treatment of pneumococcal pneumonia.

This paper is presented to show the effect of erythromycin in the treatment of 8 patients with lobar pneumonia due to the pneumococcus.

Method

All patients admitted to the Medical Ward Service of the Delaware Hospital with a diagnosis of pneumonia were routinely treated as follows: after the initial admission examination, bacteriologic cultures were made of the nasopharynx, sputum and blood. Erythromycin was then started according to one of three dose schedules (see below). Chest x-ray, complete blood count, and urinalysis as well as additional indicated laboratory studies were obtained within 12 hours of admission. Daily urinalysis was done. The patients were seen at least once daily by the author, and therapy was modified according to general requirements of the individual patient.

Two patients were stuporous or vomiting and were not considered suitable for oral medication. These 2 patients were treated with another antibiotic and are not included in this series. All other patients with a clinical, x-ray, and bacteriologic diagnosis of pneumococcal pneumonia are included in this series.

Sensitivity of each pneumococcus to erythromycin was established by disc-plate technique[5] and the minimum inhibitory concentration of erythromycin was determined by a serial two-fold dilution technique ranging in concentration of 0.5 to 0.0003 micrograms of erythromycin per milliliter.

A specimen of blood was drawn from each

patient on admission and specimens of blood were obtained at various time intervals during therapy as indicated in Table II. The serum was separated and frozen at minus 5° C. until used. Two-fold serial dilutions of the serum were made and each tube was inoculated with an equal volume (0.5 ml.) of a 1:100 dilution of an 18 hour tryptose phosphate broth culture of the pneumococcus isolated from the patient according to a modification[6] of the technique of Schlichter.[7]

CASE FINDINGS

All cases had initial temperature of 102° F. or greater. White blood cell counts on admission ranged from 8,000 to 30,000 (with five above 20,000), and in each case there was a marked shift to the left in the differential smear. Seven cases had positive sputum cultures for pneumococcus, two of which had positive blood cultures for pneumococcus. One patient who produced no sputum had a positive nasopharyngeal culture for pneumococcus.

The dosage schedule and the clinical course of each patient are shown in Table 1.

Five patients had a rapid return to normal temperature, relief of symptoms and an uncomplicated recovery. Hospitalization varied from 7 to 14 days in this group, and chest x-ray was normal on discharge in 4 of these patients, the fifth patient clearing uneventfully as an out-patient. In Case 1, there was a considerable clearing of the pneumonia in three days with symptomatic relief. However, urinary albumin increased from 1+ to 4+, and finally granular casts appeared on the second day. The possibility of a nephro-

TABLE 1

Pneumococcal Pneumonia Treated With Erythromycin

Case	Age	Site	Pneumococcus Type	Blood Culture	Dosage	Days of Treatment	Return to Normal Temperature	Hospital Days	Remarks
1	24	RLL	14	Negative	400 mgs every 6 hours	6	30 hours	9	Erythromycin stopped, penicillin started on third day.
2	20	LLL	14	Positive	400 mgs. every 6 hours	8	30 hours	10	None
3	40	LLL	3	Negative	400 mgs. every 6 hours	24	16 days	26	Delayed Resolution
4	50	LLL Empyema	3 1	Negative Negative	400 mgs. every 6 hours	8 28	30 hours	40	Pneumococcus type 3 isolated (nasopharynx) on admission. Pneumococcus type 1 isolated on 15th day. Penicillin therapy started on 17th day.
5	52	RUL	1	Negative	400 mgs. initial 200 mgs. every 6 hours	9	30 hours	14	Chest x-ray normal in 24 days.
6	69	RML	1	Positive	400 mgs. initial 200 mgs. every 6 hours	17	7 days	22	Delayed resolution
7	35	RLL	1	Negative	200 mgs. initial 100 mgs. every 4 hours	9	30 hours	14	None
8	59	RLL	3	Negative	200 mgs. initial 100 mgs. every 4 hours	6	6 hours	7	None

toxic effect of the antibiotic was considered, and therapy with erythromycin was stopped on the third day, at which time albuminuria was diminishing. Penicillin was given for three additional days.

There were two patients with delayed resolution. In Case 3 small loculated areas of effusion developed which cleared without aspiration by the 26th hospital day. In Case 6, in whom pneumococcal bacteremia had been present, some infiltration remains in the previously consolidated area ten weeks after admission and further studies are in progress on this case in the Out-Patient Department.

Case 4 is of sufficient interest to be presented in detail:

A 50 year old male was admitted with the diagnosis of pneumonia of the upper segments of the left lower lobe. He had had chest pain and cough for four days prior to admission. A pneumococcus type 3 was isolated from the nasopharynx, sensitive to erythromycin in a concentration of 0.0003 micrograms per ml. He had no sputum and blood culture showed no growth. He received 400 mgs. of erythromycin every six hours for eight days. His temperature returned to normal in thirty hours. His admission white blood cell count of 26,000 with a marked increase in percentage of polymorphonuclear leucocytes gradually fell to 14,000, with percentage of polymorphonuclear leucocytes less marked. His lungs cleared progressively by physical examination and chest x-ray evidence, and the pneumonia was considered fairly well resolved at the time of discontinuation of erythromycin.

Over the next five days signs of pulmonary consolidation increased and he again developed fever and leukocytosis. Chest x-ray twelve days after admission demonstrated an empyema. Erythromycin therapy was reinstituted. The initial aspiration of the empyema two days later yielded a purulent exudate which when cultured showed a pneumococcus type 1, not previously isolated, resistant to erythromycin by the disc technique, and resistant in a concentration of 63 micrograms per milliliter by tube dilution of erythromycin. This pneumococcus type 1 was demonstrated to be sensitive to penicillin by the disc technique. Erythromycin was stopped, and penicillin was substituted. Local treatment of the empyema included frequent aspiration with instillation of penicillin and Varidase.* He was discharged on the fortieth hospital day with essentially normal chest x-ray.

BACTERIOLOGIC FINDINGS

Pneumococci were not obtained on sputum culture of any patient after 48 hours of treatment. Table 2 illustrates the minimum inhibitory dilution of the serum against the pneumococcus isolated from each case.

It is apparent from this data that a highly effective serum concentration of erythromycin was attained in seven cases. In Case 8, this single determination is satisfactory evidence of an effective antibiotic level by the criteria of Schlichter.[7] The pneumococcus type 3 isolated from the nasopharynx of Case 4 is probably of no significance in view

TABLE 2

Minimum Inhibitory Dilution of Serum Against Pneumococci

Erythromycin Dosage	Case	Pneumococcus Type	Sensitivity to Erythryomycin in Micrograms Per Milliliter	On Admission	Minimum Serum Dilution Showing Inhibition of Pneumococcus						
					Hours After Initial Dose				Hours After Multiple Doses		
					2	3	4	6	3	4	6
400 mgs. every 6 hours	1	14	0.03								1:64
	2	14	0.015	0		1:128		1:64			
(Capsules)	3	3	0.003	0		1:64		1:32			1:64
	4	3	0.0003			1:128		1:32	1:128		1:128
	4	1	63.0					0			
400 mgs. initially	5	1	0.008	0	1:264		1:28	1:64			
200 mgs. every 6 hours (tablets)	6	1	0.002	0						1:128	1:128
200 mgs. initially	7	1	0.002	0						1:264	
100 mgs. every 4 hours (tablets)	8	3	0.008	0						1:4	

*Varidase is the registered trademark employed by Lederle Laboratories for Streptokinase-streptodornase.

of the complication produced by a different organism (pneumococcus type 1).

DISCUSSION

This series of cases is too small to justify significant conclusions, and results are essentially similar to those reported by Smith and others,[2] and Haight and Finland.[3] Of significance is the demonstration of a resistant pneumococcus appearing in Case 4. This patient had an initially favorable response which suggests that the pneumococcus type 1, though not isolated on admission, was sensitive to erythromycin.

Resistance of the organism developed during therapy with erythromycin in: one case of subacute bacterial endocarditis due to *Streptococcus salvarius* (2), two cases of staphylococcal endocarditis (3), and one case of subacute bacterial endocarditis due to *Streptococcus mitis* (4).

In addition, Heilman[4] reported development of resistance of *Staphylococcus aureus* in osteomyelitis, and Smith[2] reported development of resistance of hemolytic streptococci in an abscess of the jaw. Needham and Nichols[8] reported development of resistance of two strains of *Staphylococcus aureus* during therapy. This is ample evidence that an initially sensitive organism may readily develop resistance to erythromycin during therapy.

The only toxic effect of erythromycin observed in this series was a transient diarrhea in one case which was alleviated with symptomatic therapy, without discontinuing the antibiotic. A dose of erythromycin in capsules occasionally produced nausea, but nausea was not found to be associated with administration of tablets.

It is not known whether the albuminuria and cast formation of Case 1 was due to erythromycin or to the toxicity associated with pneumonia. Other investigators have not found renal toxicity to occur in association with erythromycin.[9]

Capsules of erythromycin were discontinued when coated tablets became available. Ease of administration as well as lack of nausea was noted with erythromycin tablets. Adequate serum inhibitory concentrations were achieved with each of the three dosage schedules. A dose of 200 mgs. every four or six hours would seem adequate, although this series is too small to recommend an optimal dosage schedule in the treatment of pneumonia.

The author is indebted to Dr. W. J. Holloway for the preparation of this study, to Dr. A. J. Morris for guidance in the clinical aspects of this series, to E. G. Scott for guidance in bacteriologic aspects of this paper, to Jeanette Shannon for technical assistance in bacteriology, and to the Visiting and House Staff of the Medical Department of the Delaware Hospital for their cooperation with this study.

SUMMARY

1. Eight cases of pneumococcal pneumonia treated with erythromycin are presented. Five cases had a prompt response and an uneventful recovery. Two cases had rather delayed resolution, and one case developed empyema.
2. A case is presented in which an erythromycin resistant pneumococcus was isolated during therapy.
3. Inhibitory serum concentrations of erythromycin are demonstrated.

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HESPERIDIN-C IN THE CONTROL OF EDEMA RELATED TO CARCINOMA

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Edema and ascites are often distressing symptoms in an individual with extensive inoperable or recurrent carcinoma. On occasion these conditions limit the activity of such a person when other factors might permit a more nearly normal existence for a longer time. A medication which would reduce the rate of development of edema and ascites would be beneficial. The loss of essential substances in the edema fluid, and the mechanical distress associated with the accumulation of fluid, would be reduced. Progressive edema, when it involves essential tissues, promotes a vicious cycle.

Edema production in carcinomatous patients is the result of many factors, among

which are infiltration of lymphatic and venous channels, mechanical pressure on vessels by tumor masses, low tissue and serum protein, and local action on capillary and lymphatic walls by a hypothetical toxic product released by malignant cells. The pressure of such a substance is indicated by an increase in the permeability and by a reduction of the adhesiveness of the intercellular substance of malignant cells.

In this study an attempt was made to reduce fragility and permeability in patients suffering from edema and ascites produced by a malignant lesion. Of the substances available, hesperidin, a flavanone glycoside, combined with ascorbic acid in equal proportions, seemed to give the greatest promise.*

The successful use of hesperidin for the clinical management of lowered capillary resistance has been reported by a number of investigators. Uniformly successful results were obtained by Scarborough[1] with pure hesperidin, with crude hesperidin, and with soluble citrin in the treatment of a number of cases of lowered capillary resistance from generalized vitamin deficiency. Morii[2] found that the administration of 30 mgm. of hesperidin daily decreased capillary permeability and increased capillary resistance in various clinical cases suffering from pleurisy, tuberculosis, Grave's disease, and beriberi. The curative effect of hesperidin in cases of toxic purpura and of toxic erythemas was demonstrated by Horne and Scarborough.[3] Rheumatic fever patients, according to Rinehart,[4] showed improvement in the clinical manifestations of the disease when treated with hesperidin. Griffith and Lindauer[5] reported that hesperidin and its methyl chalcone restored capillary fragility to normal in 85 per cent of hypertension patients with increased capillary fragility.

Clinical evidence tends to establish the effectiveness of hesperidin in correcting abnormal vascular integrity; however, this effectiveness can apparently be enhanced by giving vitamin C simultaneously. Rusznyak and Szent-Gyorgi[6,7] postulated that cellular vitamin C was accompanied by a substance of similar importance and related activity, and found this substance (hesperidin) associated with capillary permeability. Warter et al.[8] believe that hesperidin is essential for the absorption and retention of vitamin C, and that the two substances act interdependently in maintaining normal capillary resistance. These investigators found Hesperidin-C an effective combination in correcting capillary fragility and permeability in rheumatoid arthritis[8, 9] In a series of cases showing clinical manifestations of lowered capillary resistance and increased capillary permeability, Selsman and Horoschak[10] found Hesperidin-C to be effective in correcting the abnormalities. They postulated that hesperidin is essential to combine vitamin C with a protein fraction to form intercellular cement substance for the maintenance of normal vascular integrity. The administration of large doses of ascorbic acid and hesperidin resulted in considerable improvement in the ecchymotic lesions, and the pain they were causing, in almost all of 26 cases of leprosy treated by Mom.[11] Barishaw[12] reported that lowered capillary resistance can be successfully treated with adequate doses of Hesperidin-C.

Twenty-four patients with inoperable or recurrent carcinomas of intra-abdominal origin were selected for study. All had extensive edema or ascites. Each was given three tablets containing 50 mgm. hesperidin and 50 mgm. of ascorbic acid four times a day. Because some of the patients were followed for as long as fourteen months, it is obvious that there were changes in the diet and salt intake, and that other medications were given. At various intervals 10 patients received testosterone because it reduced their pain. Hesperidin-C was substituted, with the diet and salt intake kept as constant as possible during comparative periods of evaluation. For a limited time 16 patients received mercurial diuretics, which gave moderate temporary relief to 4 but soon lost effect.

Ascites was the most prominent symptom in 10 patients, all of whom showed some improvement with the medication. Two patients that previously required bi-weekly paracentesis were completely controlled by the combination of hesperidin and vitamin C. The rate of development of ascites was reduced by more than one-half in all patients. A reduction in the feeling of abdominal compression was noted by all within forty-eight hours.

*Hesperidin-C: Supplied by Steven Horoschak, Medical Research Department, National Drug Company, Philadelphia 44, Pa.

Ankle and leg edema constituted the chief complaint in fourteen patients. Two patients stopped the medication after a two weeks' trial because of no improvement. Six patients showed an excellent result with edema appearing only in the late evening, after many hours of walking. Two patients, who had been in bed 80% of the day with marked sacral and leg edema, were able to remain out of bed 60% of the day, and showed only low ankle edema. The level of edema dropped from the knee to the ankle in two patients who were ambulatory twelve hours of the day.

COMMENT

It is remarkable that greater physical comfort and improved sense of well-being were experienced by 22 of 24 patients receiving Hesperidin-C. Whatever the mechanism of action, any medication that advances the comfort of patients with advanced malignant lesions is of value. Objectively, there was some improvement in all but two of the patients. In 12 of the 24 patients there was an improvement in the ambulatory status. Edema reduction, with concomitant improvement in nutrition and function, prolongs the time during which these patients can get about and can be self-sufficient.

This preliminary report is offered so that other investigators may try Hesperidin-C in similar conditions to evaluate its ability to reduce edema.

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MISCELLANEOUS

Secretary's Letter No. 266 Sept. 11, 1953 Says Dr. Lull

Many of you, like myself, must have read this recent press association story with raised eyebrows:

"DENVER — President Eisenhower went to an osteopath Friday for treatment of a sore arm that has bothered him for nearly a month."

The third paragraph of the story said he was accompanied by his personal physician, Dr. Howard M. Snyder.

Delaware Academy of Medicine

The Executive Committee wishes me to inform you of certain new services which have been made available to members of the Academy:

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You are invited to inspect the exhibit of old surgical and dental instruments recently installed on the first floor of the Academy building.

I urge your continued use and support of your Academy of Medicine.

Sincerely Yours, Lemuel C. McGee, M. D.
President

+ Editorials +

DELAWARE STATE MEDICAL JOURNAL

Owned and published by the Medical Society of Delaware, a scientific society, non-profit corporation. Issued on the fifteenth of each month under the supervision of the Committee on Publication.

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Subscription price: $4.00 per annum, in advance. Single copies, 50 cents. Foreign countries: $5.00 per annum.

Vol. 25 October, 1953 No. 10

The Home Folks Agree

Our September editorial, "Lowering the Standards," showing the lamentable drop in the standards of medical licensure in the State of New York, was published with a modicum of fear that we were, in a fashion, merely a voice in the wilderness, perhaps a lone voice. Not so! Since our publication, we are now beholding article after article and editorial after editorial taking the same note of censure and sympathy that we took. Witness this editorial from the New York State Journal of Medicine for October 15, 1953:

Medical Education

On July 1, 1953, "the educational requirements for internship," which have long been a part of the present New York State education law, were amended to allow hospitals to appoint interns without regard to their educational background whatsoever. Not only does the new law permit the employment of interns with questionable medical training, but also State and municipal hospitals may obtain residents on the same basis.

This amendmen does more than to lower pre-existing medical standards; it abrogates them. The committee which studied the intern problem in the State and which made the recommendations upon which the new law is based was composed of representatives, among others, of members of the hospital councils of the State and of Greater New York and the medical schools. The latter were outnumbered and, with one particular exception, were nonvocal.

Thus their recommendations reflect to a large extent the point of view of hospital administrators. These latter were faced with a pressing and seemingly insolvable problem. There are slightly more than 5,600 approved internships and residencies in the State of New York. The internships are only about 50 per cent filled, and many hospitals obtained none for the current year. The intern deficit is not only a local but a national phenomenon. It stems from two sources, namely, that the number of positions far exceeds the number of graduates and the demands of the armed services have eliminated the two-year internship. The committee was told, and it was generally agreed by the representative administrators, that many institutions would be forced to curtail their services were a way not found to provide interns. Furthermore, the committee was quite well aware of the fact that the old law which required that an intern be a graduate of an approved school was not being enforced. Thus the motivation and excuse for its abolition existed. A ready supply of man power to fill the void could be found among graduates of the unapproved Latin, South American, Continental, and Asiatic schools. Many such graduates were already employed in open violation of the existent law. This was the easy answer, and it is not surprising that it was forthcoming. Under the guise of a graduate medical education program it assumed an international, nonisolationist cloak of respectability.

Thus the Legislature has given a pragmatic answer to the very difficult problem of supplying the hospitals with cheap medical labor. In so doing, as is often the case with pragmatism, standards have been sacrificed. The internship is now part of the American medical scene. In the beginning it was designed as a supplemental year of practical medical education. Because of its nature but definitely as a corollary, the internship furnished patient service without very much cost. Unfortunately, we now face a situation where in many instances service has become the predominant issue. Hospitals say they cannot function without such labor, nor can they afford to pay for value received except through their educational programs.

Unfortunately the degree of M. D. does not miraculously bestow the qualifications of a medical teacher upon its recipient. Real educators in this field as in all fields require special talents and training. They are rare and equally so are the desirable graduate medical educational programs. Our own graduates choose those internships whose programs furnish really advanced educational opportunities. Such programs in themselves are expensive and are usually, although not always, associated wth centers of medical learning. Patient service is present even in these but is of secondary import. Close supervision, often described in graduate programs, does not alone furnish medical education of ad-

vanced quality any more than close supervision by the average public accountant would yield graduate opportunities in the field of mathematics.

The Legislature, faced on the one hand with the demand on the part of the hospitals for cheap labor and on the other with the failure of our own graduates to be enticed by "educational opportunities" of doubtful value, has furnished an answer of opportunism. To achieve this, past standards have been eliminated. That the old law was not enforced can be no possible excuse, nor is it conceivable that unrealistic educational programs can be of any great benefit to foreign physicians whose basic medical training is so faulty as to preclude any possibility of licensure. We must face reality and admit that failing to find sufficient interns from our own schools, we have now embarked on a course of exploitation of foreign graduates. Once these graduate recognize this fact, our foreign relations will have been poorly served indeed.

Some day we must come to grips with the basic problem and furnish the general run of hospitals with the type of help they require at a cost they can afford. There are not now, nor will there be, sufficient qualified graduates to fill all the internships. The use of unqualified graduates is at best a temporary measure of expediency. A survey should be made of the type of service needed. Perhaps it is largely technical and under close supervision might be furnished by properly qualified and trained nurses or special technicians.

It is hoped that in the future legislators will be better and more thoroughly advised. Medical standards are of long and difficult achievement. Their relaxation means public suffering. Let us neither sacrifice them to expediency nor with lofty idealism ignore the plight of our hospitals but rather, with thought, wisdom, and foresight, attempt to solve our basic problem.

Delaware Academy Of General Practice

The Delaware Academy of General Practice will hold its second annual Scientific Session on Saturday, 12 December 1953, at the Delaware Academy of Medicine auditorium. We have been fortunate to secure the following excellent speakers:

Dr. Herman K. Hellerstein, of Cleveland, Ohio, (the William Urie Memorial Lecture); Dr. James L. A. Roth, of University of Pennsylvania Graduate School; Dr. Meyer Naide, of University of Pennsylvania; Dr. A. Lee Lichtman, of New York Postgraduate Medical School; Dr. Jacob J. Weinstein, of George Washington University; Dr. Donald Stubbs, of George Washington University; Dr. Thomas Durant, of Temple University; Dr. Elmer Hess, of Erie, Pennsylvania.

The Scientific Session will start at 10:00 a.m. promptly, and each speaker will be allotted 30 minutes to present his paper followed by 10 minutes of discussion.

The business meeting of the Delaware Academy of General Practice will start at 9:00 a.m. promptly, for election of officers for 1954. Luncheon will be served in the library for those who wish to attend.

At 7:30 p.m. Dinner will be served at the Brandywine Country Club as the Annual Subscription Banquet and Ball. Dr. John S. DeTar, Speaker of the House of Delegates of the American Academy of General Practice, will be the guest speaker at the banquet. Dancing will follow until 1:00 a.m.

Tickets for the Banquet and Ball may be obtained from Dr. Harold A. Tarrant, 1315 West 9th Street, Wilmington. The subscription is $15.00 per couple, and since the capacity of the Brandywine Country Club is limited, tickets will go on a "first come, first served" basis.

If you have attended any of the functions of the Delaware Academy of General Practice in the past you can expect as fine a program and as wonderful a dinner and party as can be obtained.

BOOK REVIEW

THE EPIDEMIOLOGY OF HEALTH. A New York Academy of Medicine Book. Iago Galdston, M. D., Editor. Pp. 197. Cloth. Price, $4.00. New York: Health Education Council, 1953.

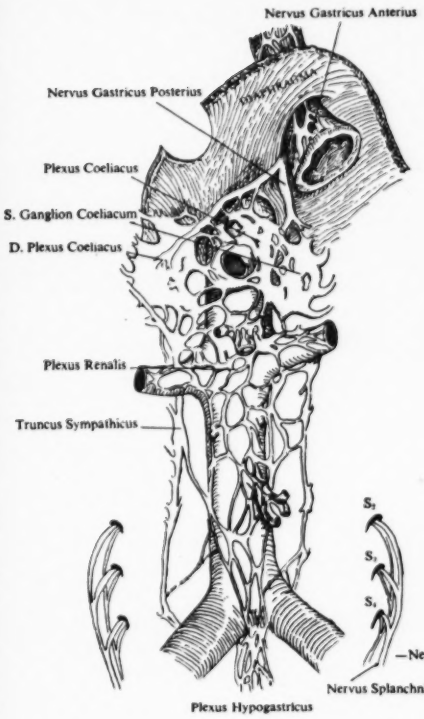
This very enlightening book gives a new public health orientation concept which is based on the present trends in health thinking and practicing. The material is based on the Eleventh Annual Eastern States Health Education Conference.

The application of this concept of the "epidemiology of health" in clinical medicine, in public health, and in health education will yield effective results if the principles elaborated in the fifteen chapters of this book are applied in the propagation of health.

Several authors discuss the evolution of the epidemiology of health as contrasted to the epidemiology of disease, and point out how it is practiced in the armed forces, in industry, in medical practices, in education, and in the control of such public health problems as tuberculosis, mental hygiene, and nutrition.

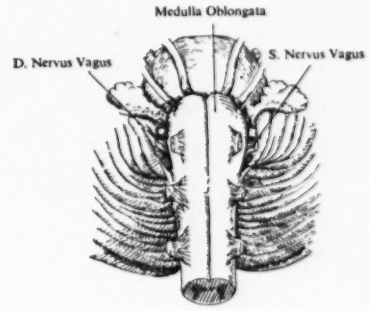
The material is well organized, very frankly presented, and the theme of the book is well emphasized, so that the reader realizes that "health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

This book is highly recommended to physicians and medical students, as well as to public health workers.



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1. Zupko, A. G.: Pharmacology and the General Practitioner, GP 7:55 (March) 1953.

2. McHardy, G. G., and Others: Clinical Evaluation of Methantheline (Banthine) Bromide in Gastroenterology, J.A.M.A. *147*:1620 (Dec. 22) 1951.

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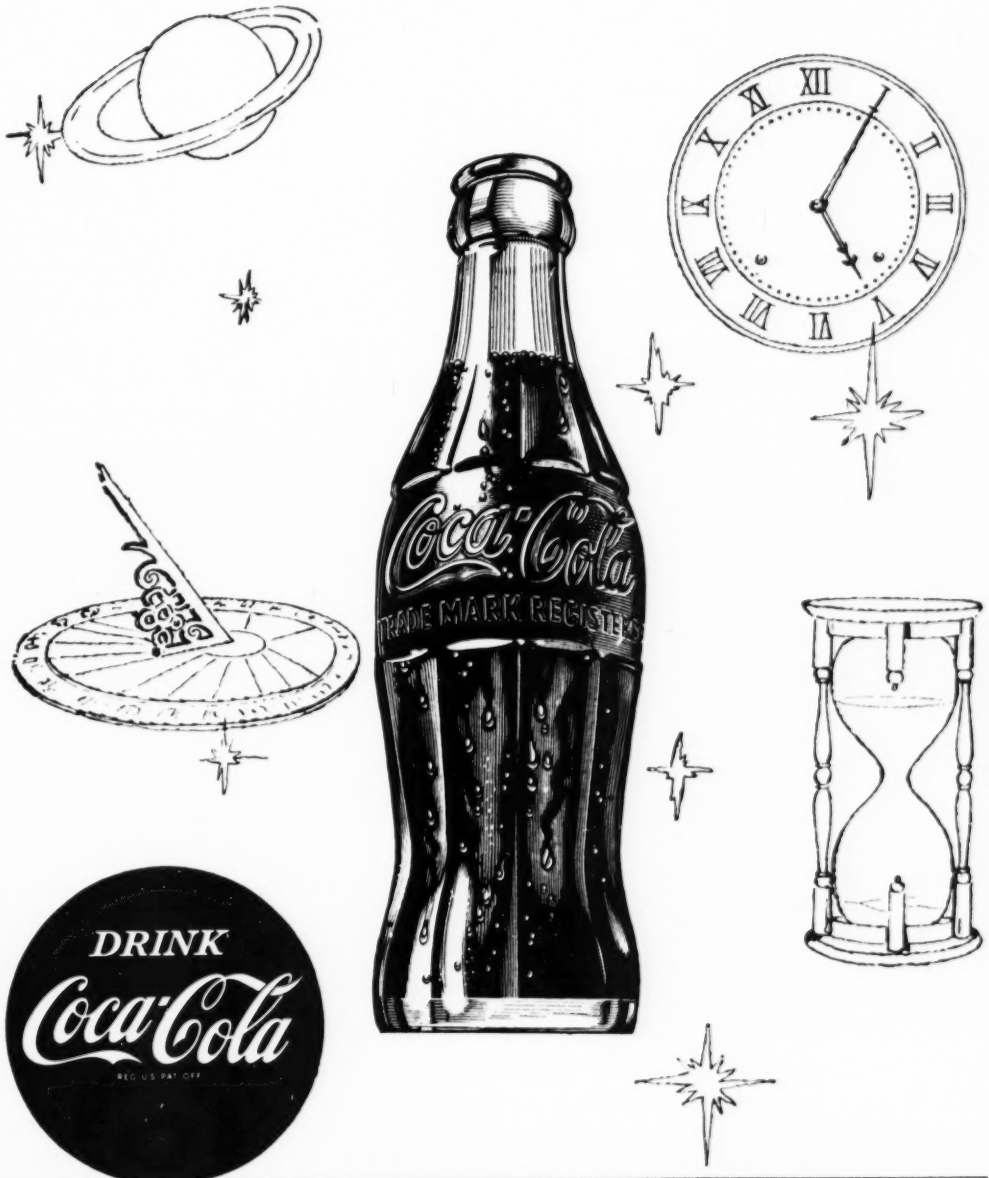
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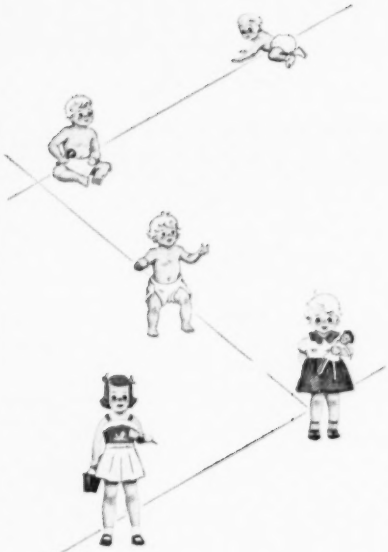
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